Supplementary Information

The Role of L-Proline and Co-Catalysts in the Enantioselectivity of OXA-Michael-Henry Reactions

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Materials and methods

Reagents and solvents were purchased as reagent grade and used without further purification. All nuclear magnetic resonance (NMR) data were acquired in $CDCl_3$ or DMSO-d_6 on a Bruker AVANCE 400 NMR spectrometer, observing ^1H and ^{13}C at 400.13 and 100.61 MHz, respectively, or Bruker DRX 200 NMR spectrometer, observing ^1H and ^{13}C at 200.13 and 50.3 MHz, respectively. The spectrometers were equipped with a 5-mm multinuclear direct detection probe with z-gradient. All ^1H and ^{13}C NMR chemical shifts are given in ppm (δ) relative to the tetramethylsilane (TMS) signal at 0.00 ppm as internal reference and the coupling constants (J) are in Hz. Thin layer chromatography (TLC) was performed using silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, stained with iodine vapor or acidic vanillin. HPLC analysis was performed in a Shimadzu Prominence liquid chromatography, equipped with a LC-20AT pump, SPD-M20A Photodiode Array detector, SIL-20A automatic injector and a Shim-pack C-18 VPODS 4.6_250 mm 5 lm reverse phase column. Chiral column model Astec Cellulose DMP with 4.6 mm × 25 cm and particle diameter of 5 µm. The solvents were purified according to standard procedures.

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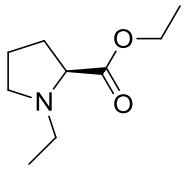
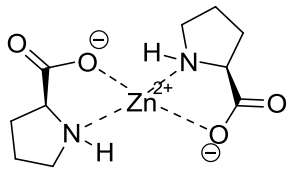
Characterization data for compound **1**

Diethyl-*L*-proline (compound **1a**)



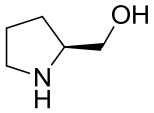
In a 50 mL flask was added 1.15 g of *L*-proline and 4.5 g of K_2CO_3 in 20 mL of ACN. Then 2.3 mL of ethyl bromide was also added in the reaction. The reaction was maintained under stirring and heating at 40 °C overnight. After the time and monitoring of product formation by CCD (MeOH:EtOAc 1:10), 30 mL of H_2O and (3×) 30 mL of EtOAc were added to extract the organic phase, dried with Na_2SO_4 and concentrated in vacuum. The product obtained was a yellow liquid in 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20 (q, *J* 7.1 Hz, 2H), 3.11-3.28 (m, 2H), 2.69-2.82 (m, 1H), 2.30-2.56 (m, 2H), 1.80-2.16 (m, 4H), 1.27 (t, *J* 7.1 Hz, 3H), 1.13 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.18, 65.99, 60.70, 53.23, 48.85, 29.49, 23.07, 14.36, 13.66.

Zn[*L*-proline]$_2$ (compound **1b**)[2,3]



The zinc amino acid complex was prepared in 50 mL flask by addition of 0.6 mL triethylamine and 4.34 mmol *L*-proline in 10 mL MeOH. After 10 min, 2.17 mmol of zinc acetate was added in the mixture. The reaction was kept under stirring and RT. After stirring for 45 min a white precipitate formed and was collected by filtration to give a 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.8 (m, 2H), 3.2-3.0 (m, 4H), 2.2-1.8 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.7, 60.9, 47.4, 30.0, 25.7.

L-Prolinol (compound **1c**)[4]



In round-bottomed flask and two 21-well shakers, coupled with reflux condenser was added 8.75 g of proline, 6.92 g of $NaBH_4$. It was transferred 200 mL of THF by siphoning, avoiding the contact of the solvent with the humidity. After, a 19.3 g solution of iodine (I_2) in 50 mL of THF was prepared. The transfer was done with the aid of an addition funnel coupled to the mouth of the flask. The reaction was placed in a 0 °C ice bath and iodine solution was added in small aliquots for 30 min. After reaction with iodine and complete formation of the hydrogen gas, the reaction was subjected to heating (approx. 40 °C) and the condenser was coupled to a water reflux pump, porcelain pieces were also added into the flask and kept under stirring overnight. After 18 h we let the reaction cool to room temperature and stirred methanol carefully until the mixture becomes clear. After stirring for 30 min, the solvent was removed by rotary evaporator, leaving a white liquid. After the elapsed time, 150 mL of 20% KOH solution was added under the white liquid and the reaction was allowed to stir for 4 h. The organic phase was extracted 3× with CH_2Cl_2, dried with Na_2SO_4 and concentrated by spin evaporator to give a yellowish liquid in 85% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.41 (s,

1H), 4.12 (dd, *J* 3.1 and 11.4 Hz, 1H), 3.66 (dd, *J* 3.1 and 11.4 Hz, 1H), 3.29-3.43 (m, 1H), 2.79-3.09 (m, 2H), 1.76-2.09 (m, 4H).

References

1. Karthikeyan, T.; Sankararaman, S.; *Tetrahedron: Asymmetry* **2008**, *19*, 2741.
2. Darbre, T.; Machuqueiro, M.; *Chem. Commun.* **2003**, 1090.
3. Zeba, N.; Siddiqui, Z. N.; Farooq, F.; *Catal. Sci. Technol.* **2011**, *1*, 810.
4. McKennon, M. J.; Meyers, A. I.; Karlheinz Drauz, K.; Schwarm, M.; *J. Org. Chem.* **1993**, *58*, 3568.

Spectra of compounds

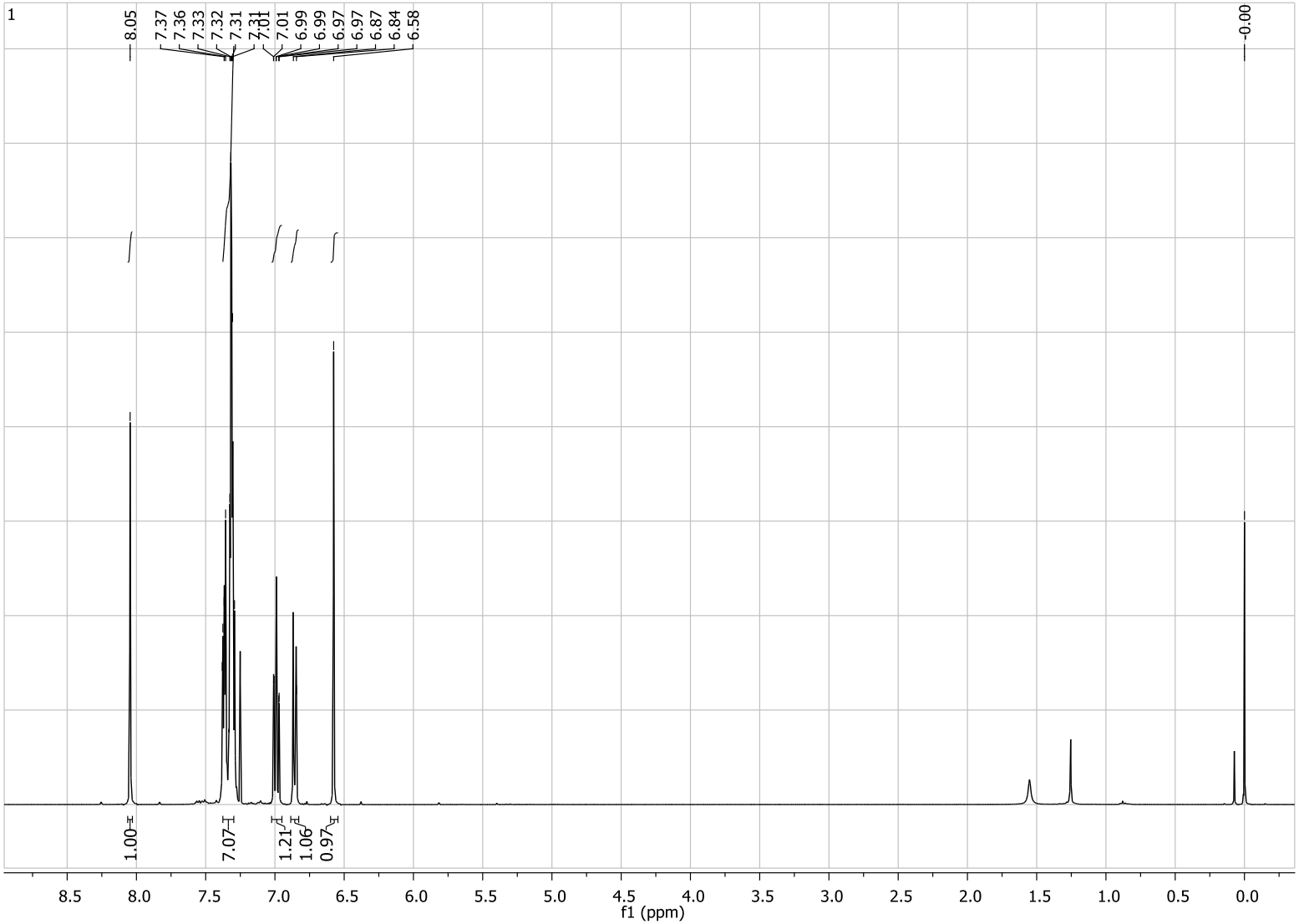


Figure S1. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4**.

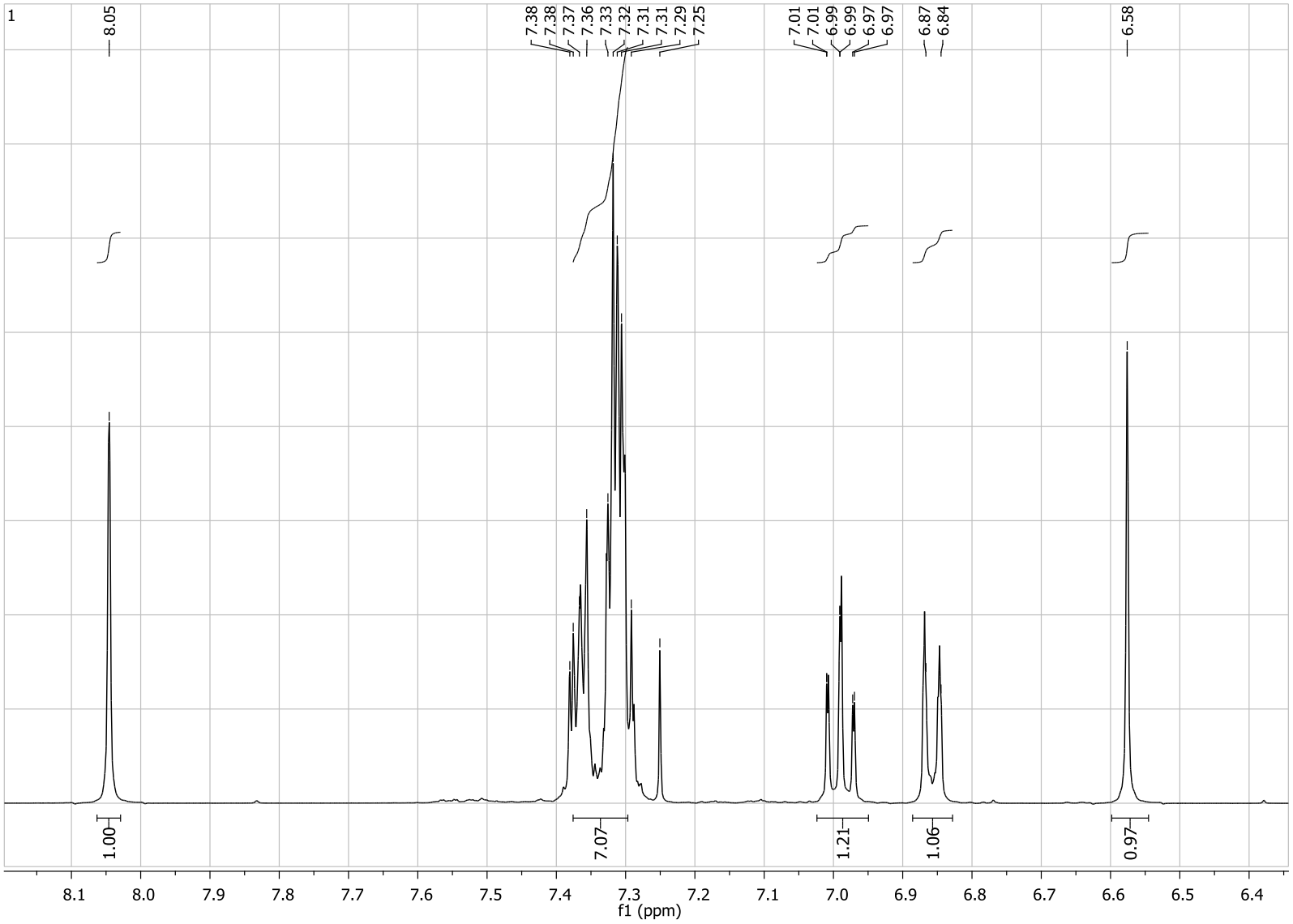


Figure S2. Expansion of ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4**.

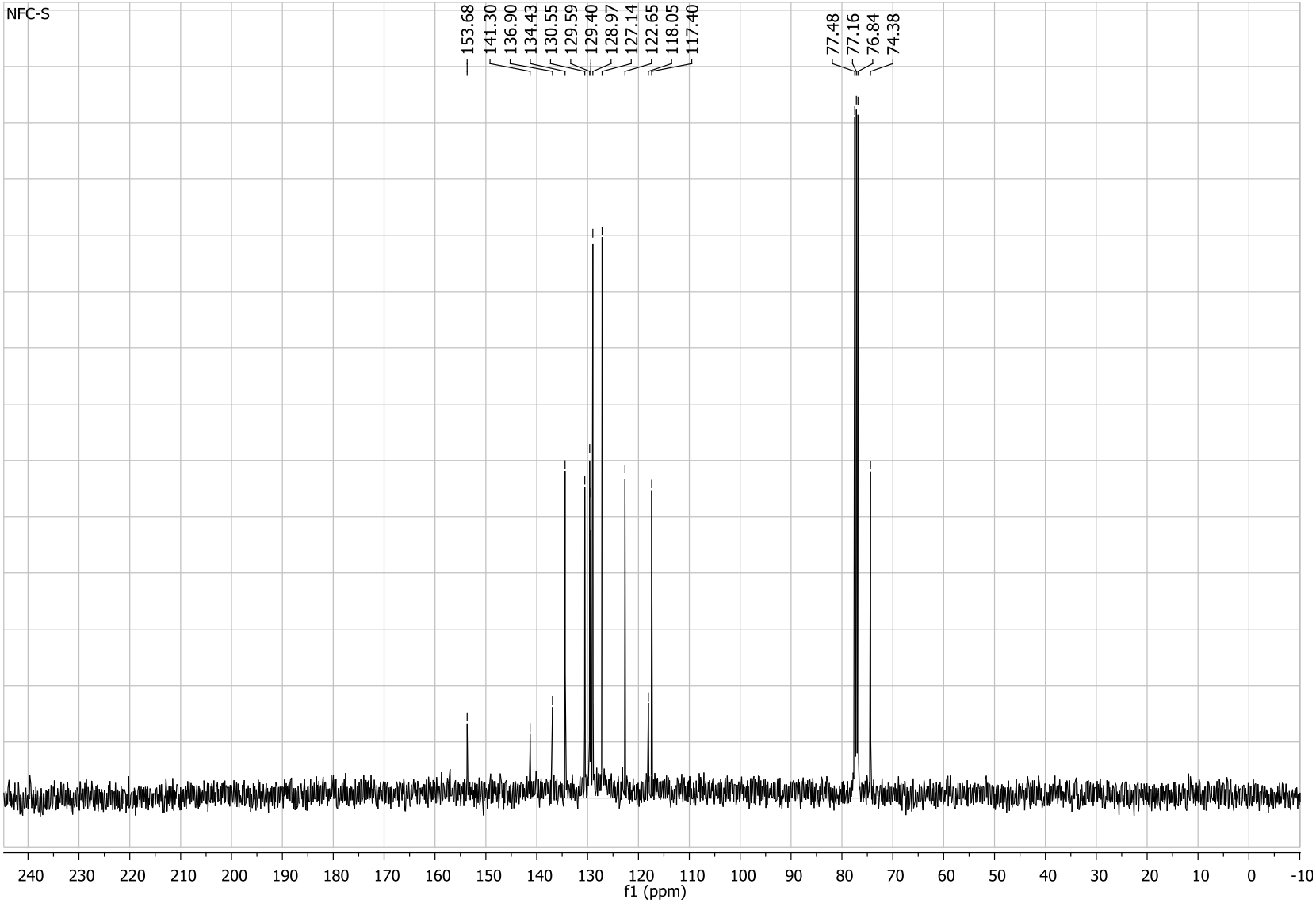


Figure S3. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **4**.

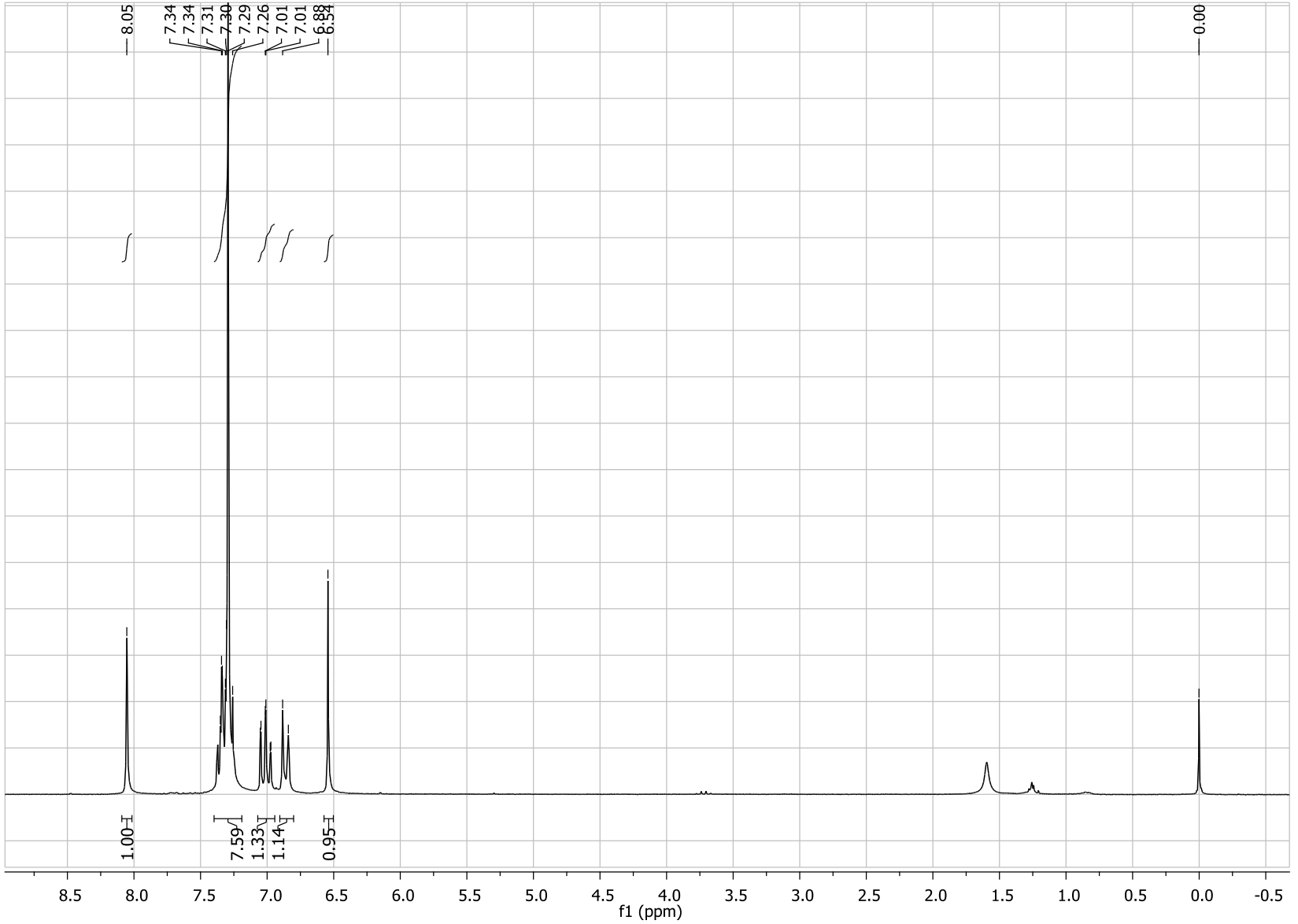


Figure S4. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4a**.

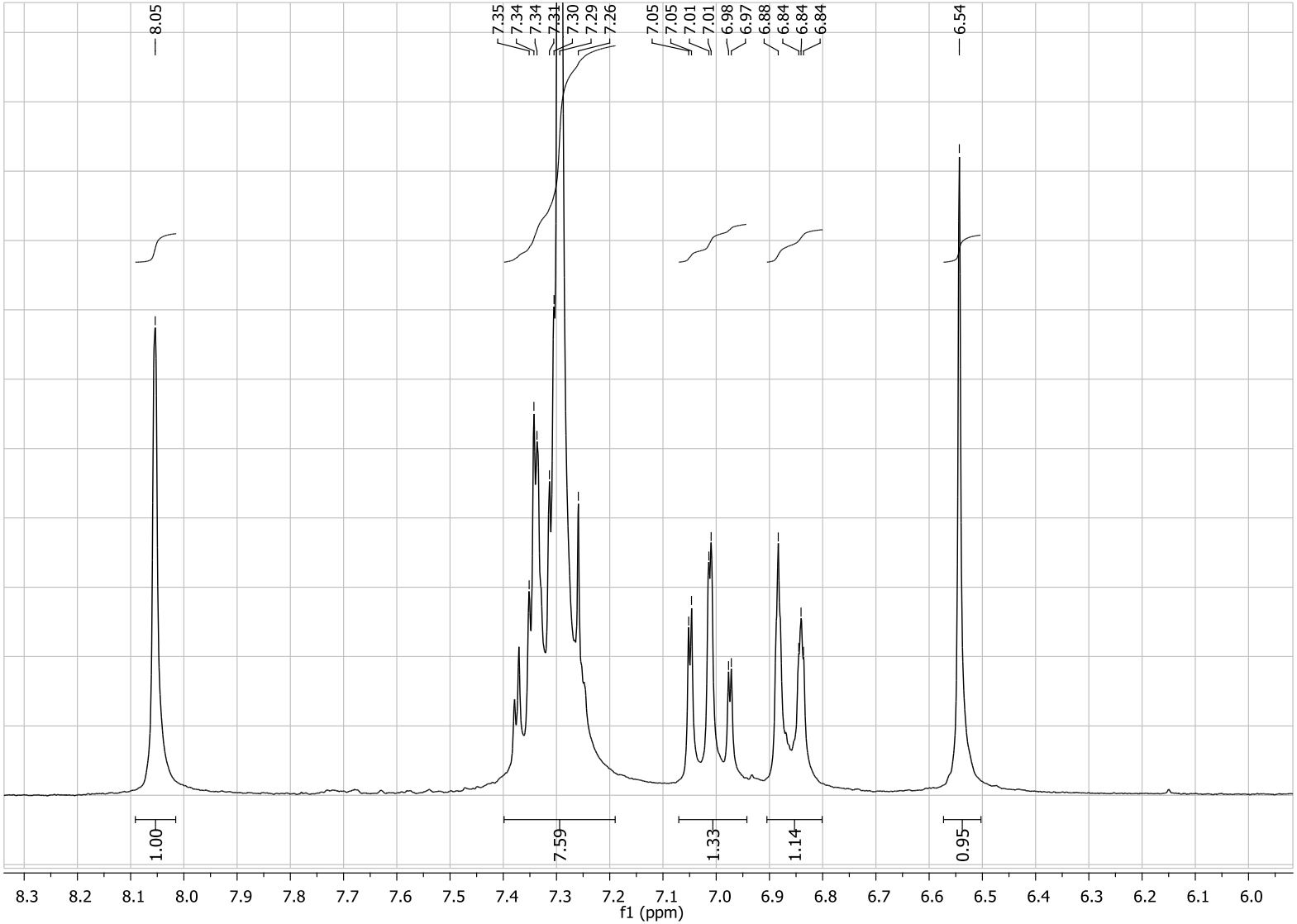


Figure S5. Expansion of ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4a**.

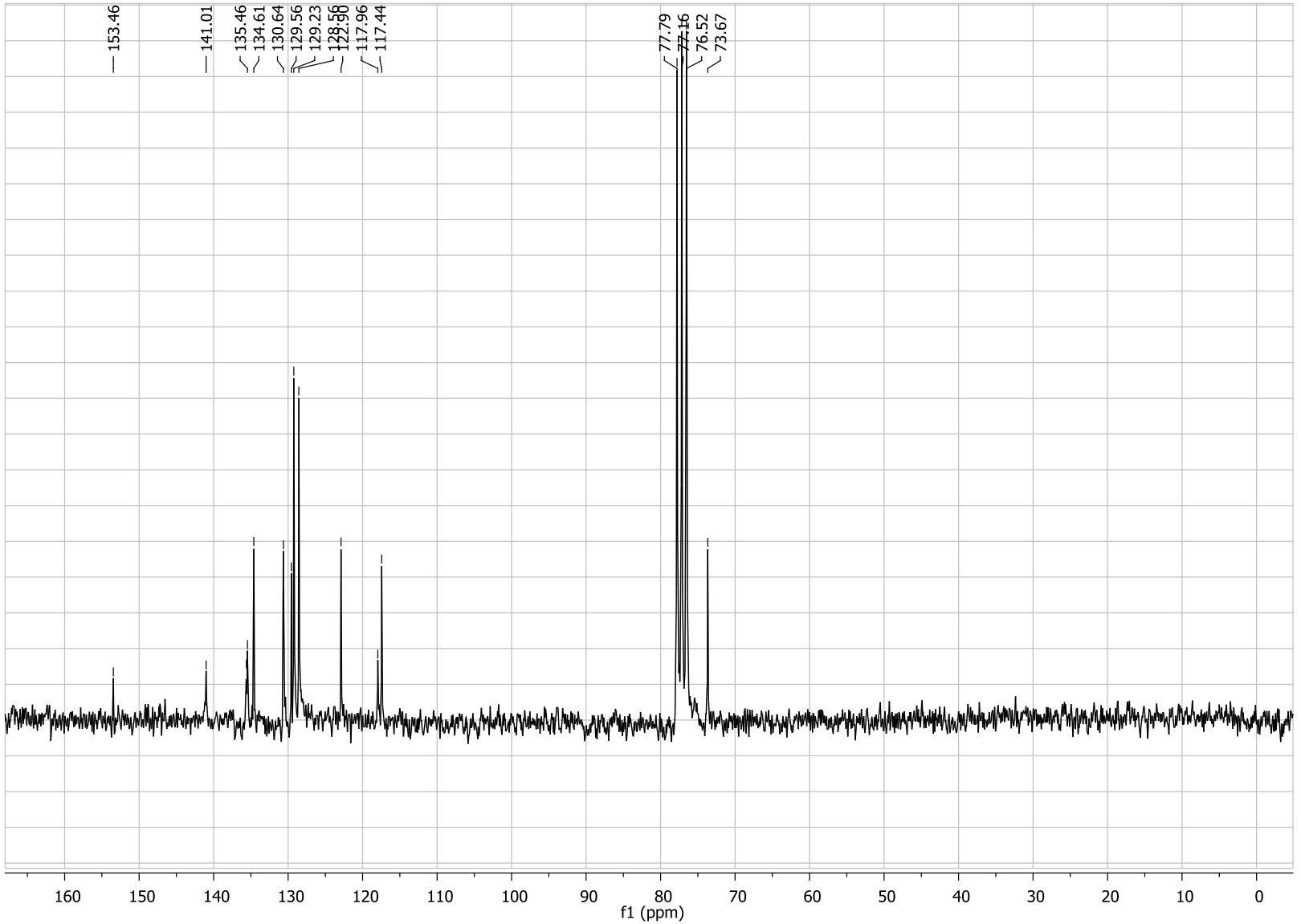


Figure S6. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **4a**.

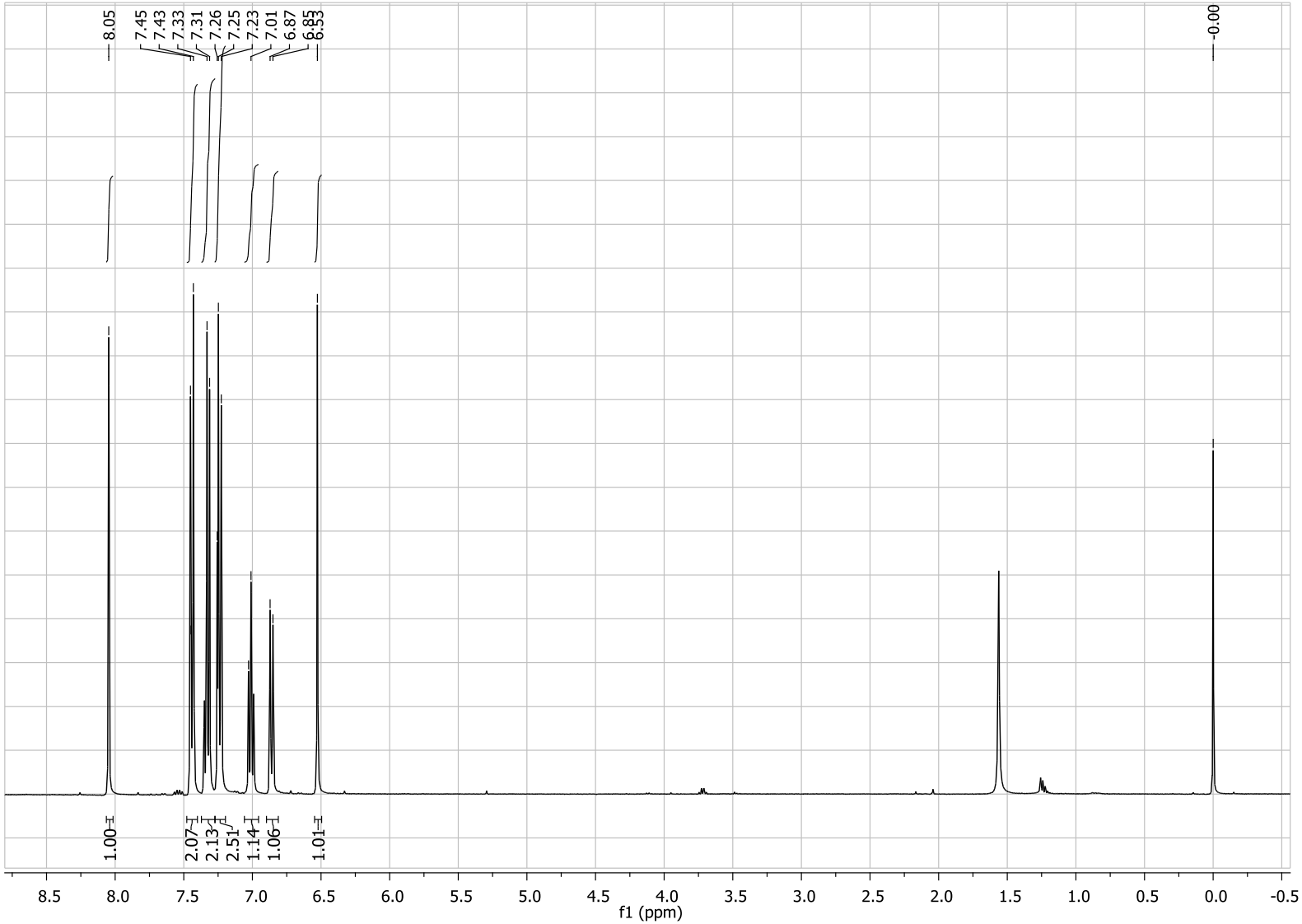


Figure S7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4b**.

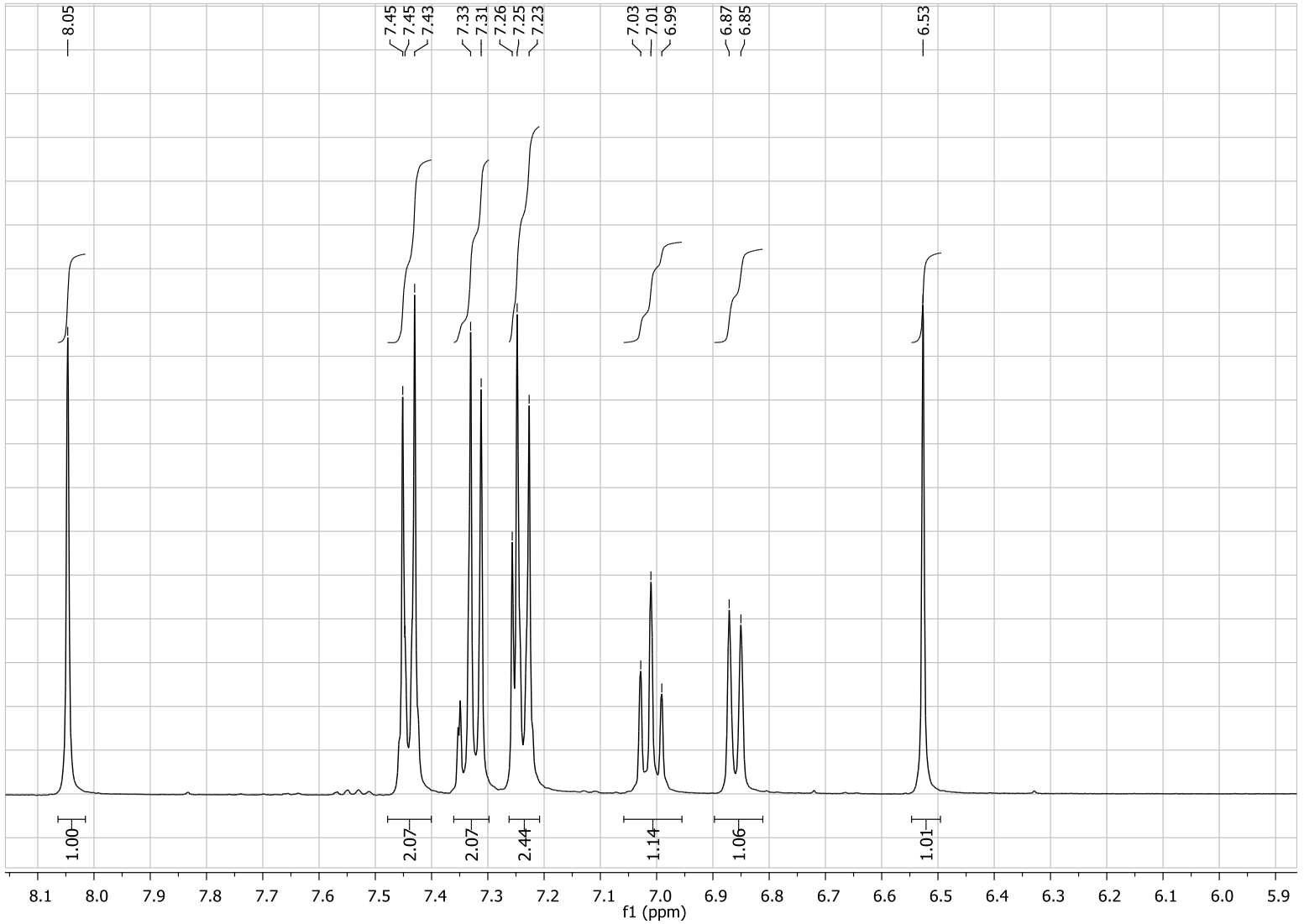


Figure S8. Expansion of ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4b**.

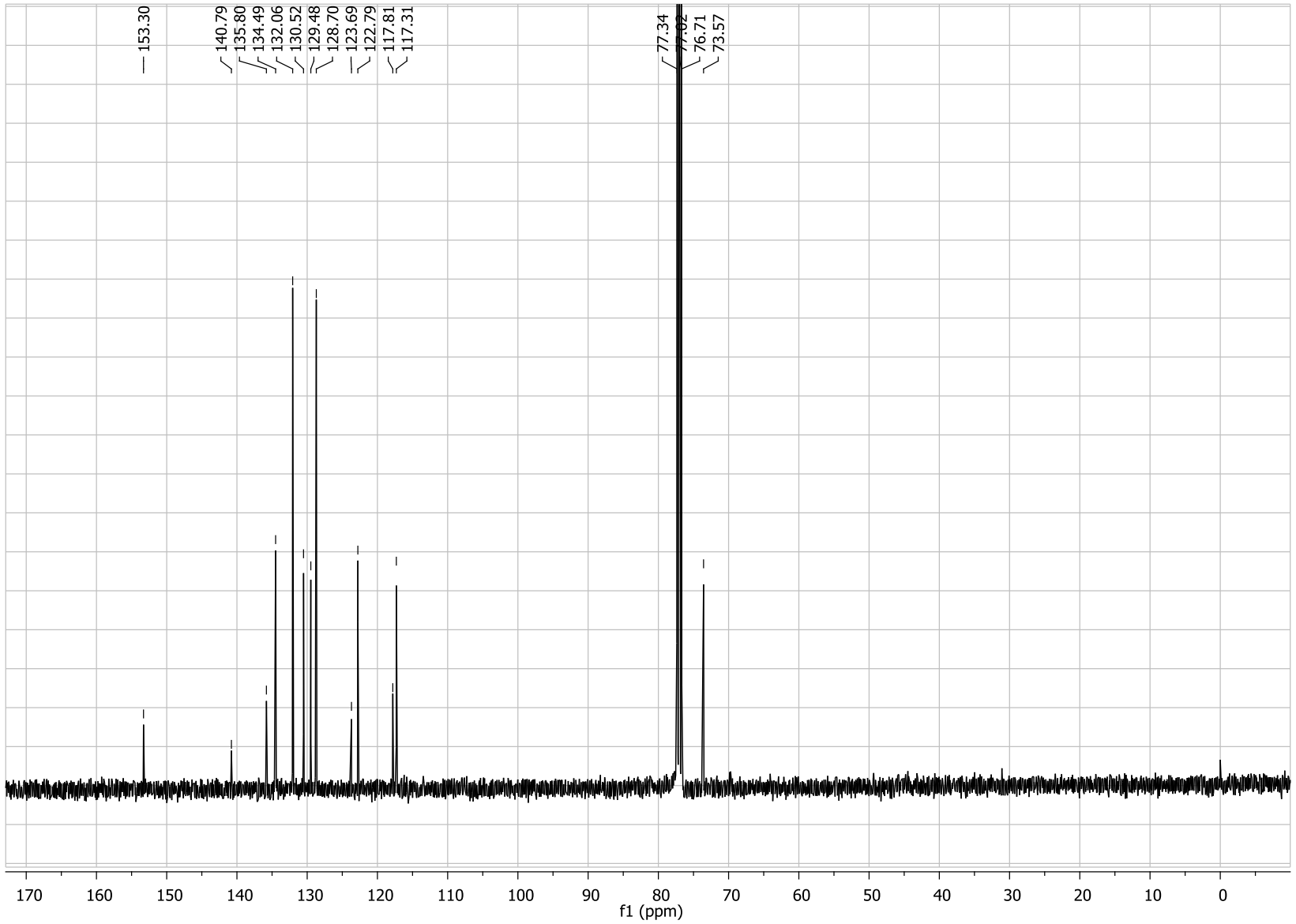


Figure S9. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4b**.

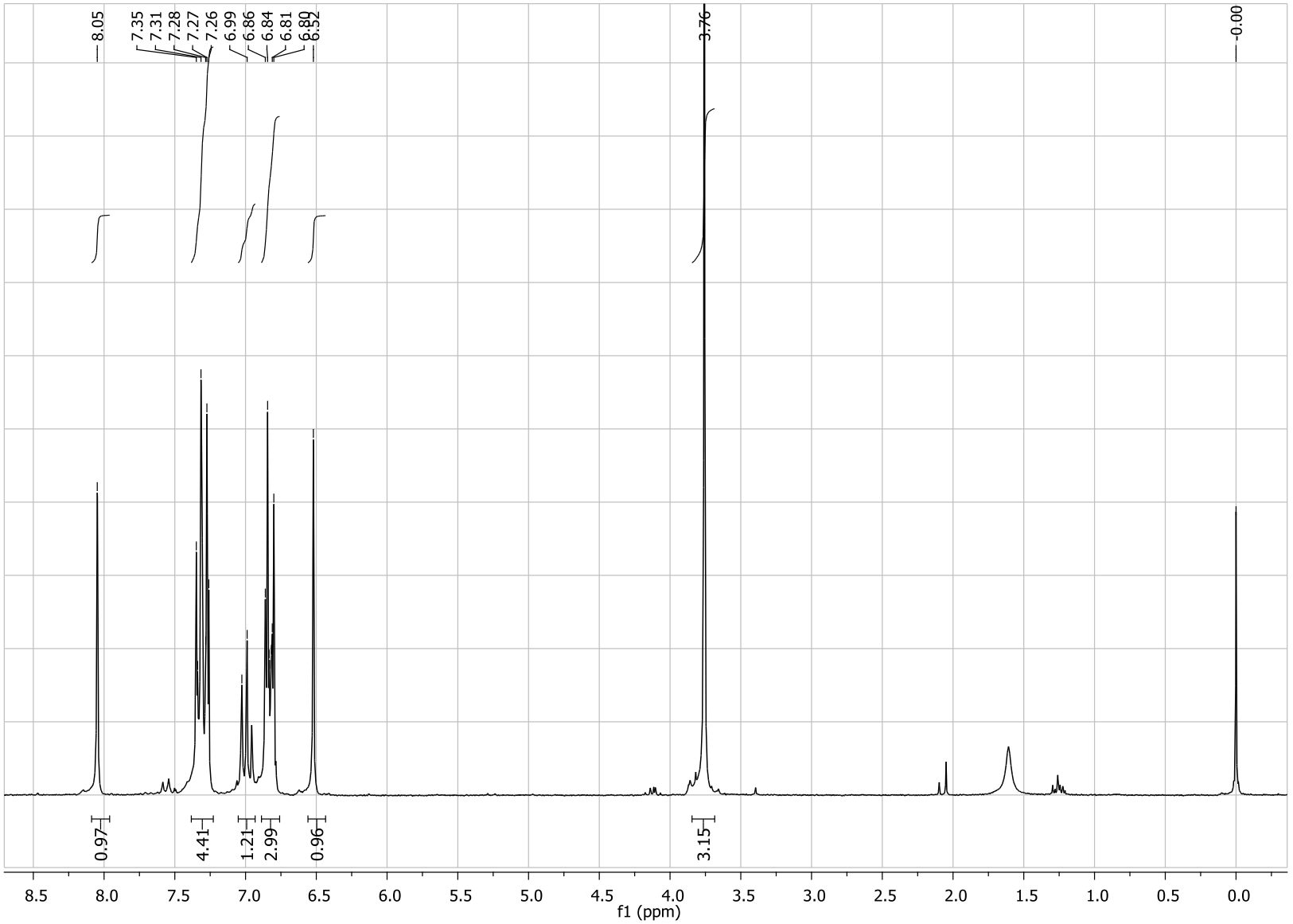


Figure S10. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4c**.

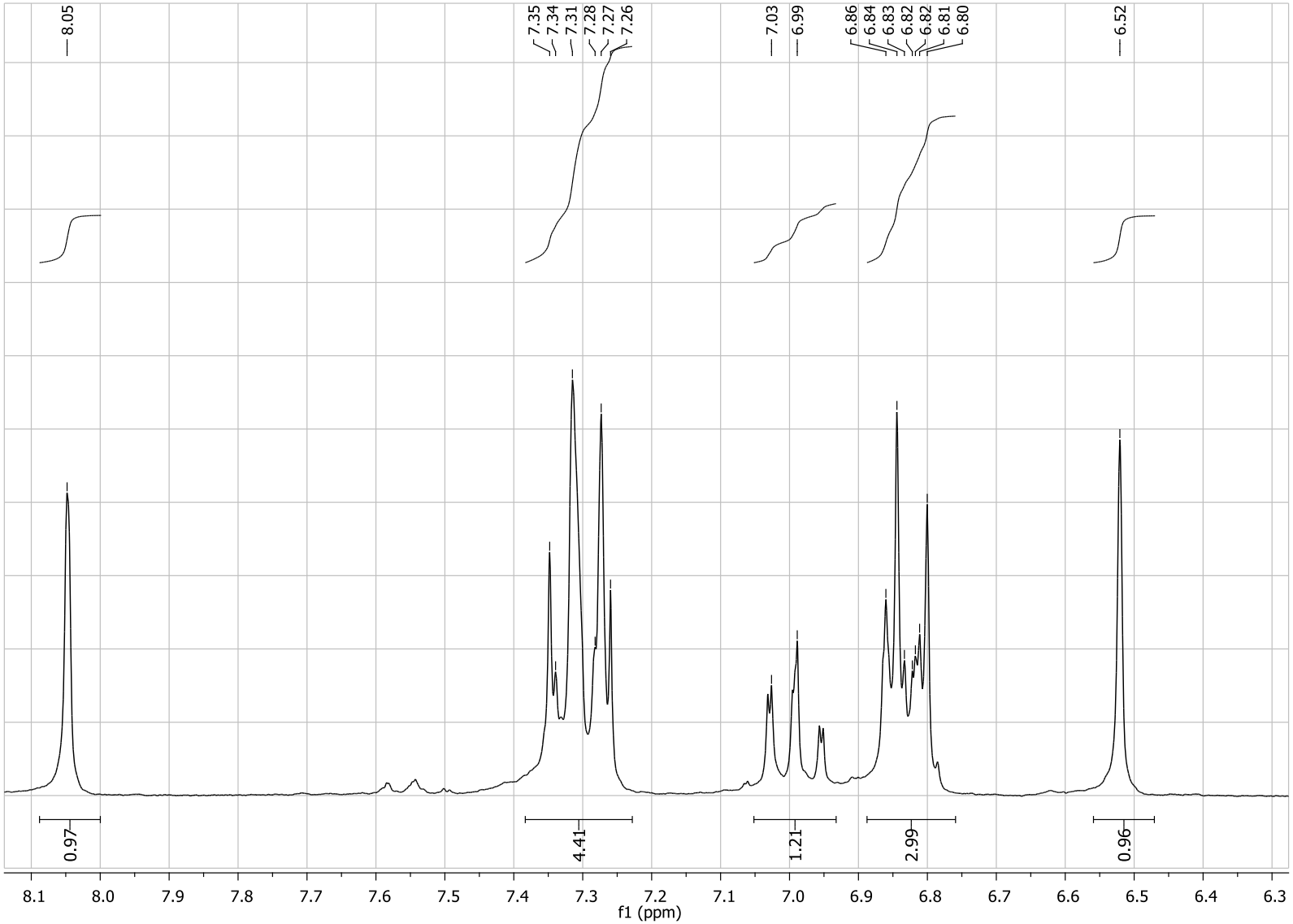


Figure S11. Expansion of ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4c**.

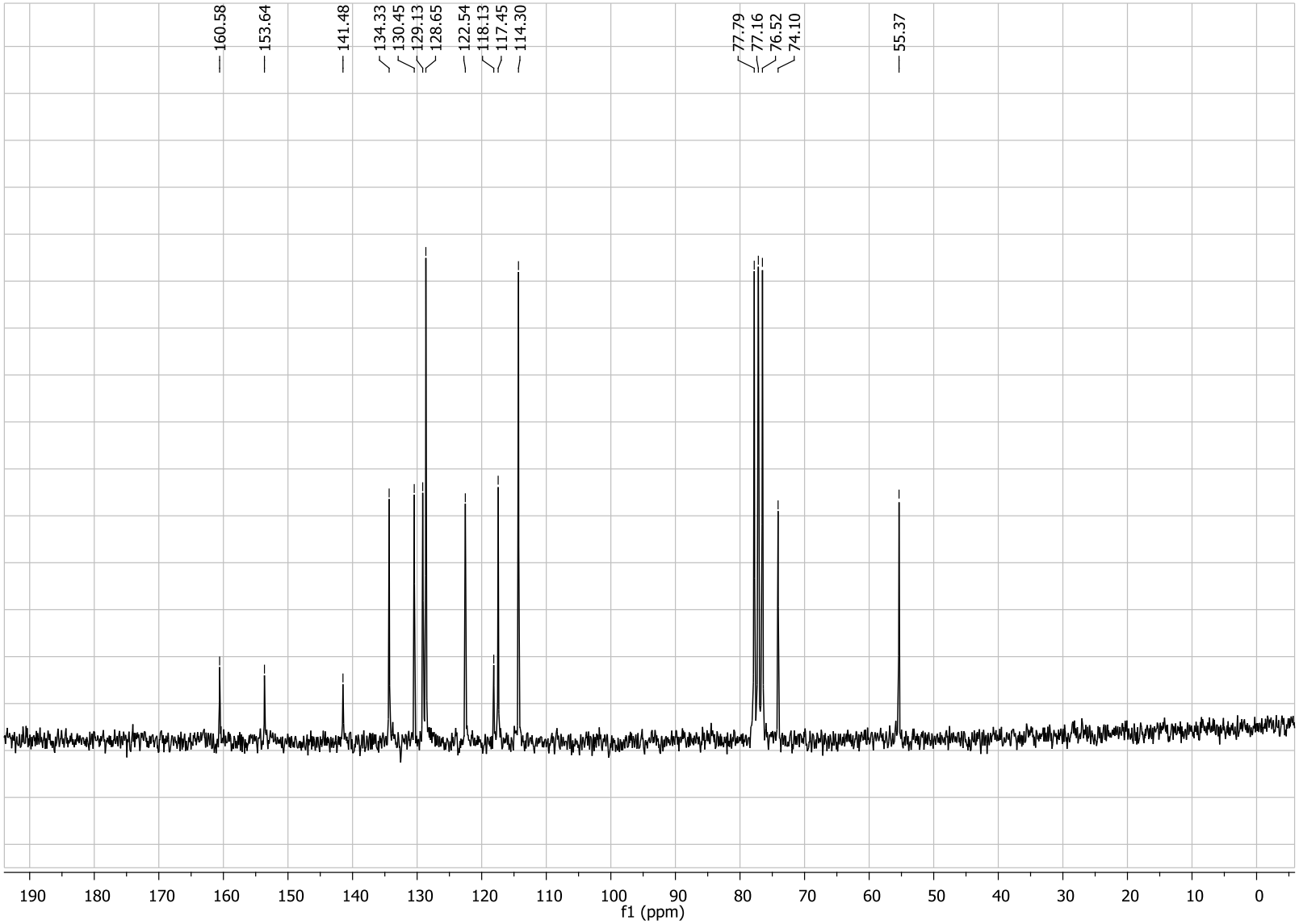


Figure S12. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **4c**.

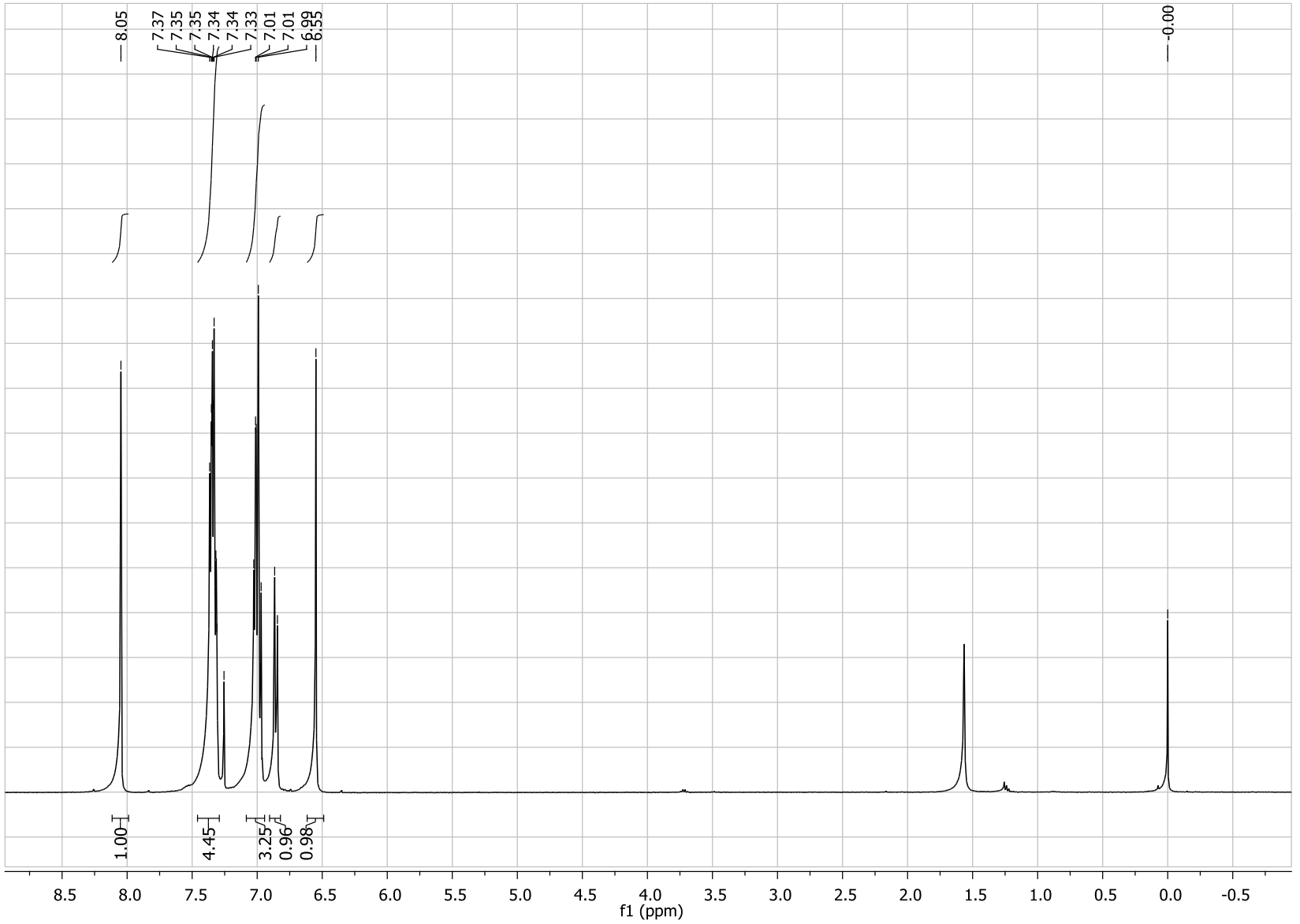


Figure S13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4d**.

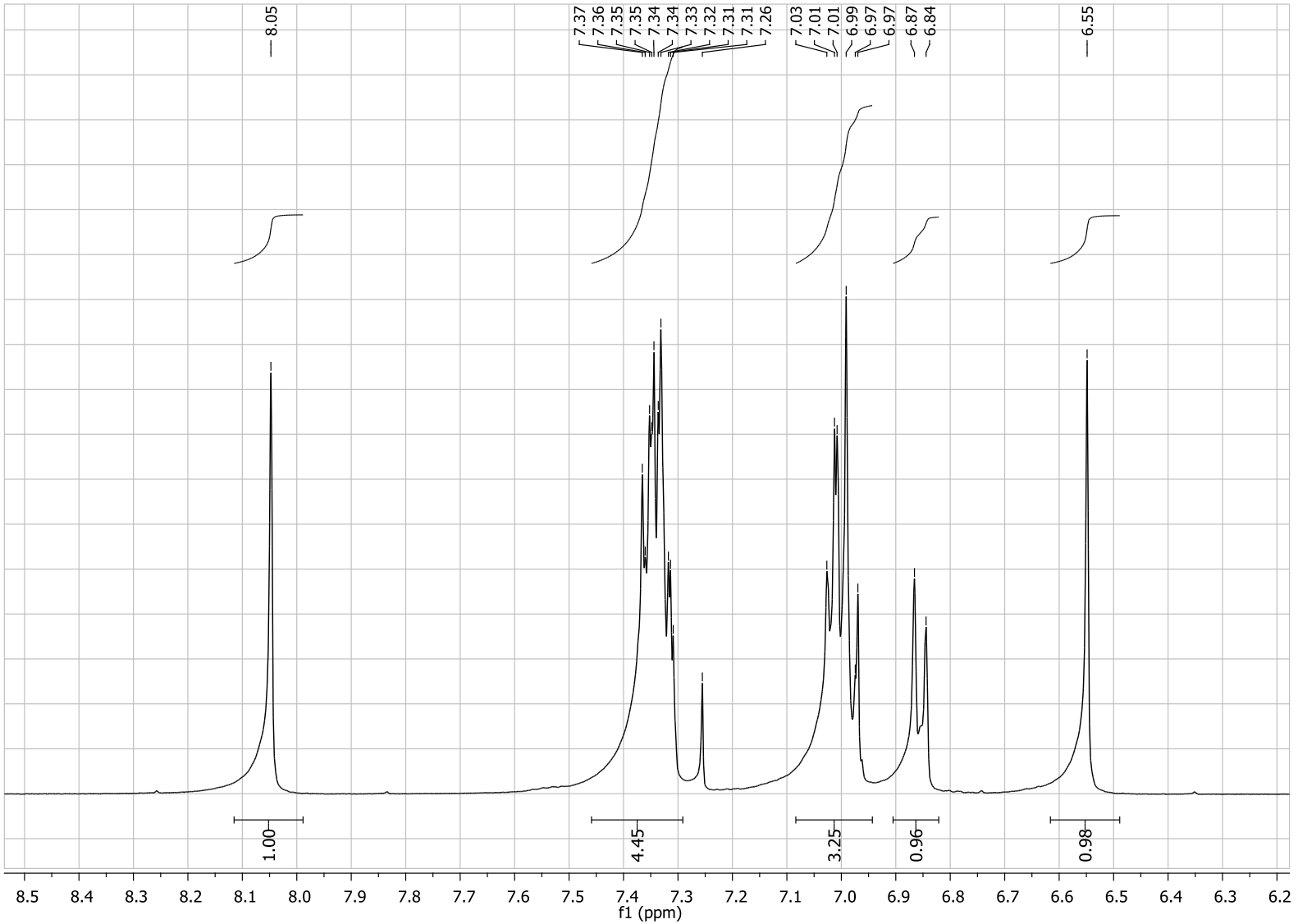


Figure S14. Expansion of ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4d**.

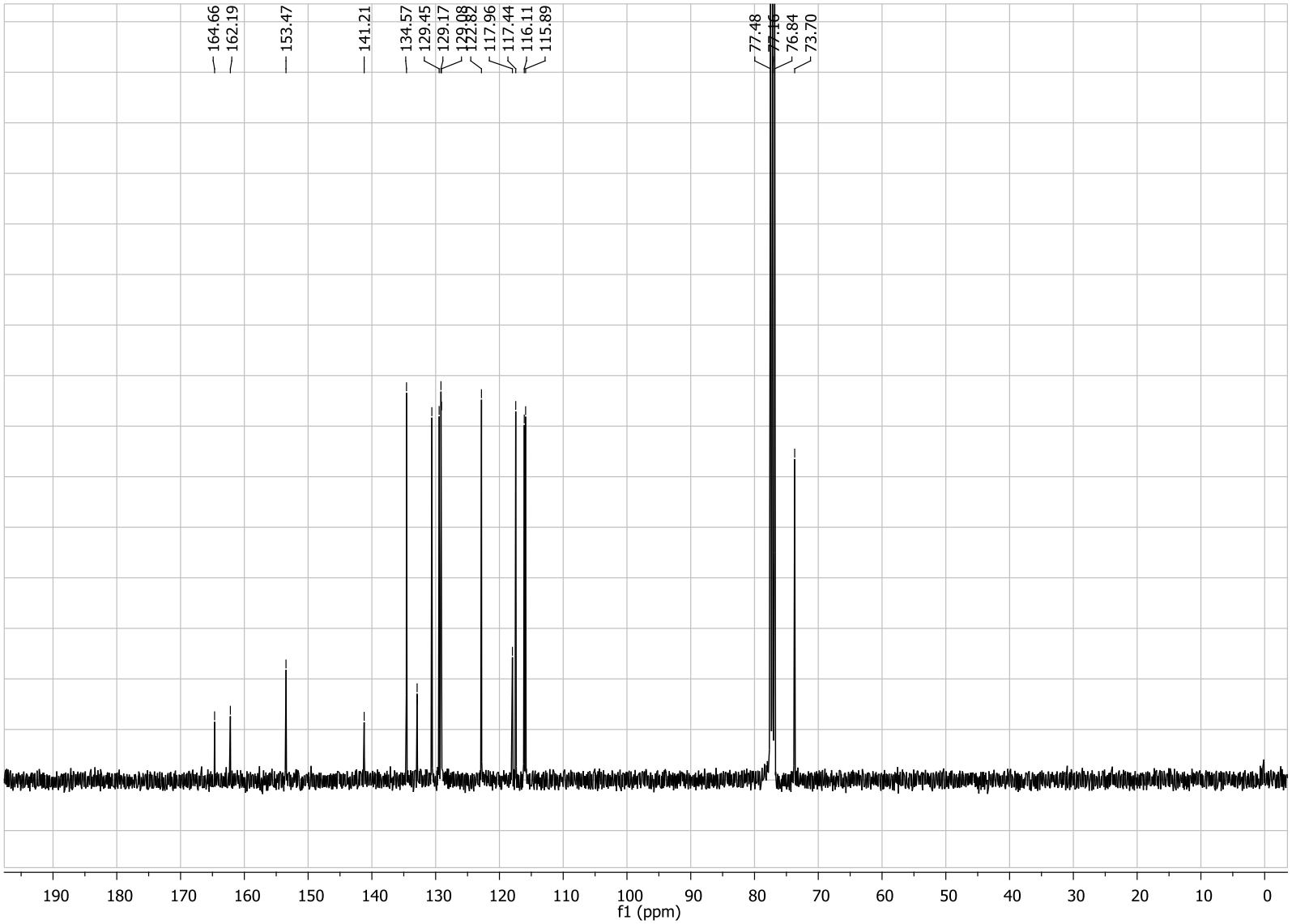


Figure S15. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4d**.

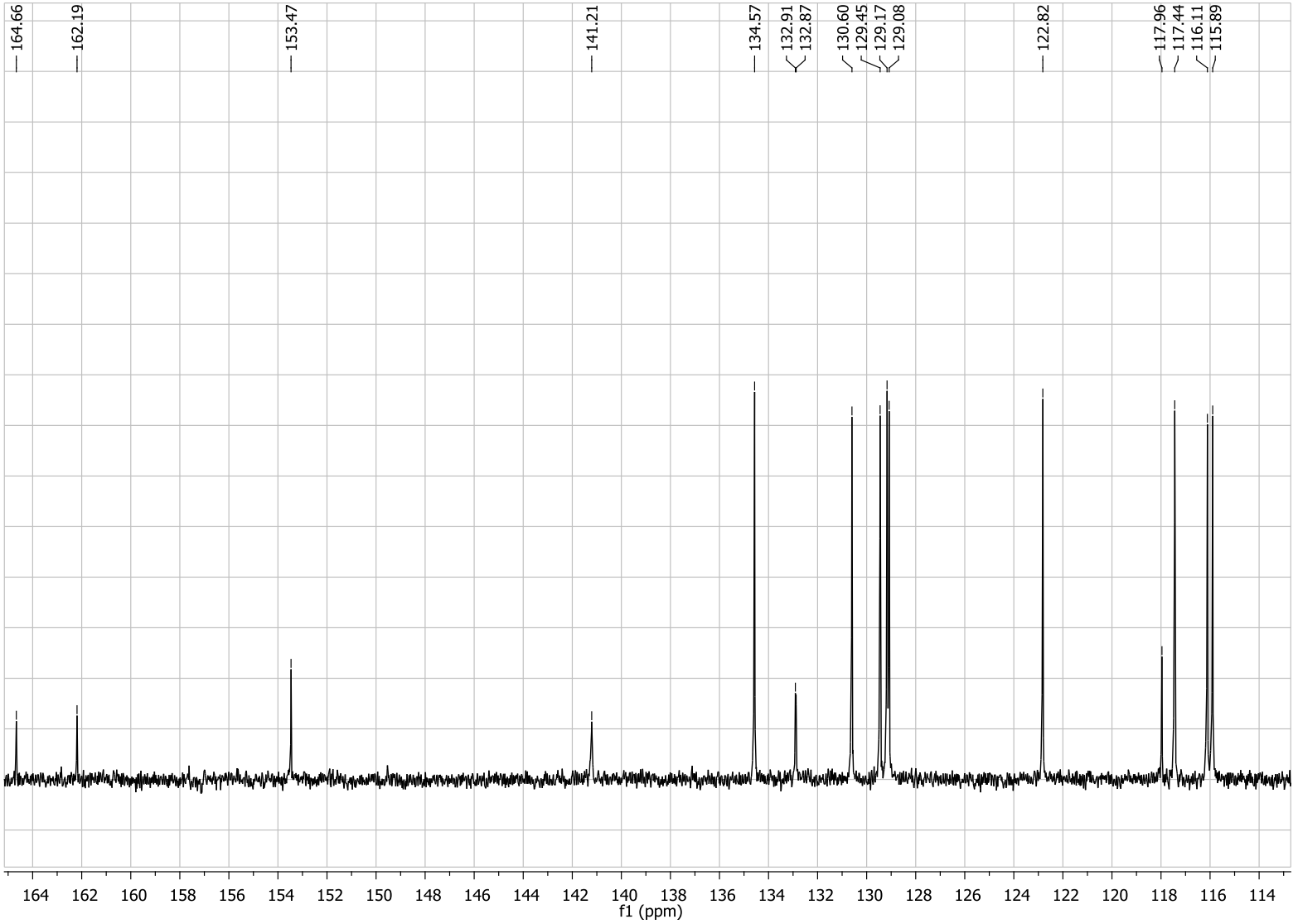


Figure S16. Expansion of ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4d**.

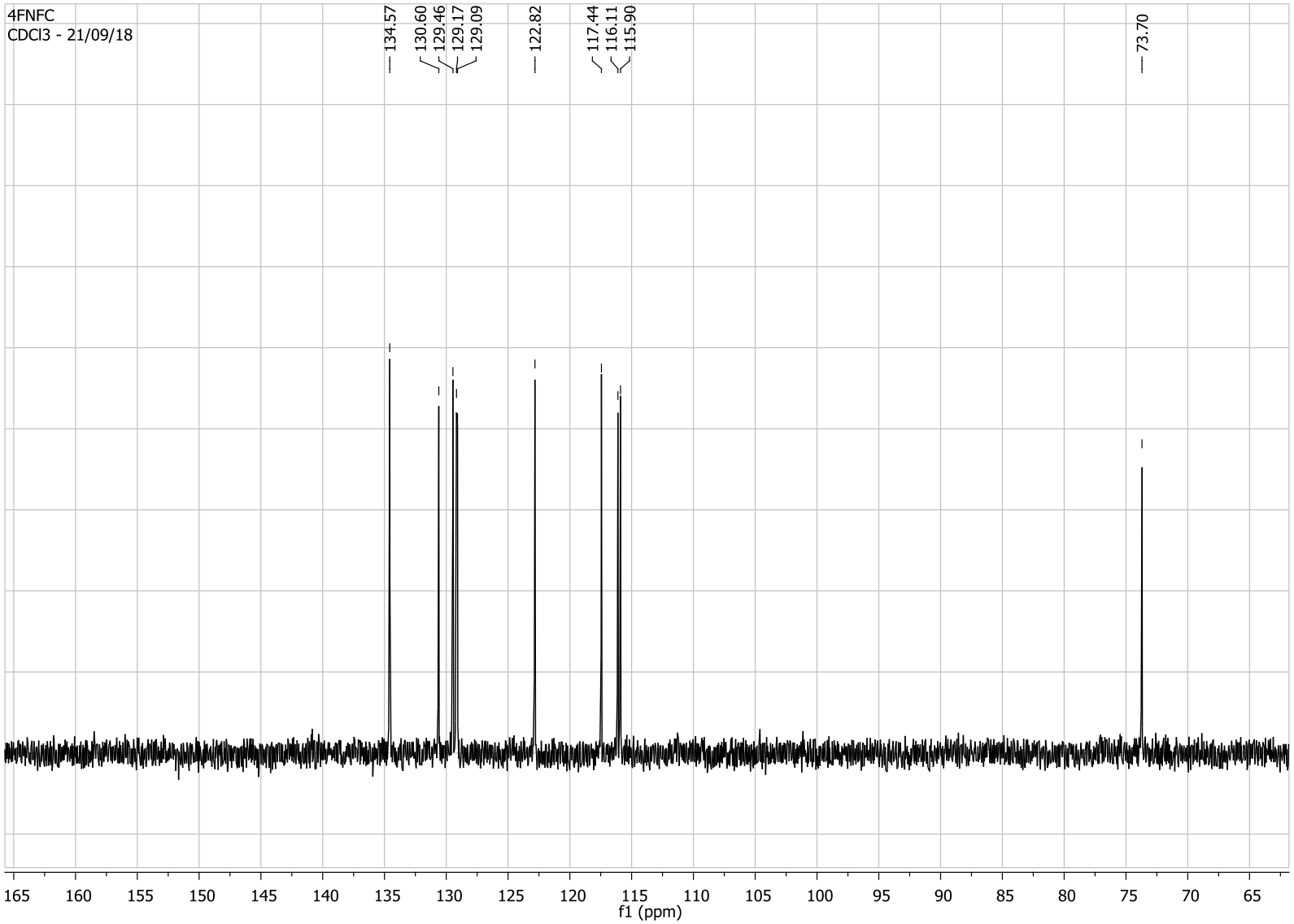


Figure S17. ^{13}C DEPT 135 NMR spectrum (100 MHz, $CDCl_3$) of compound **4d**.

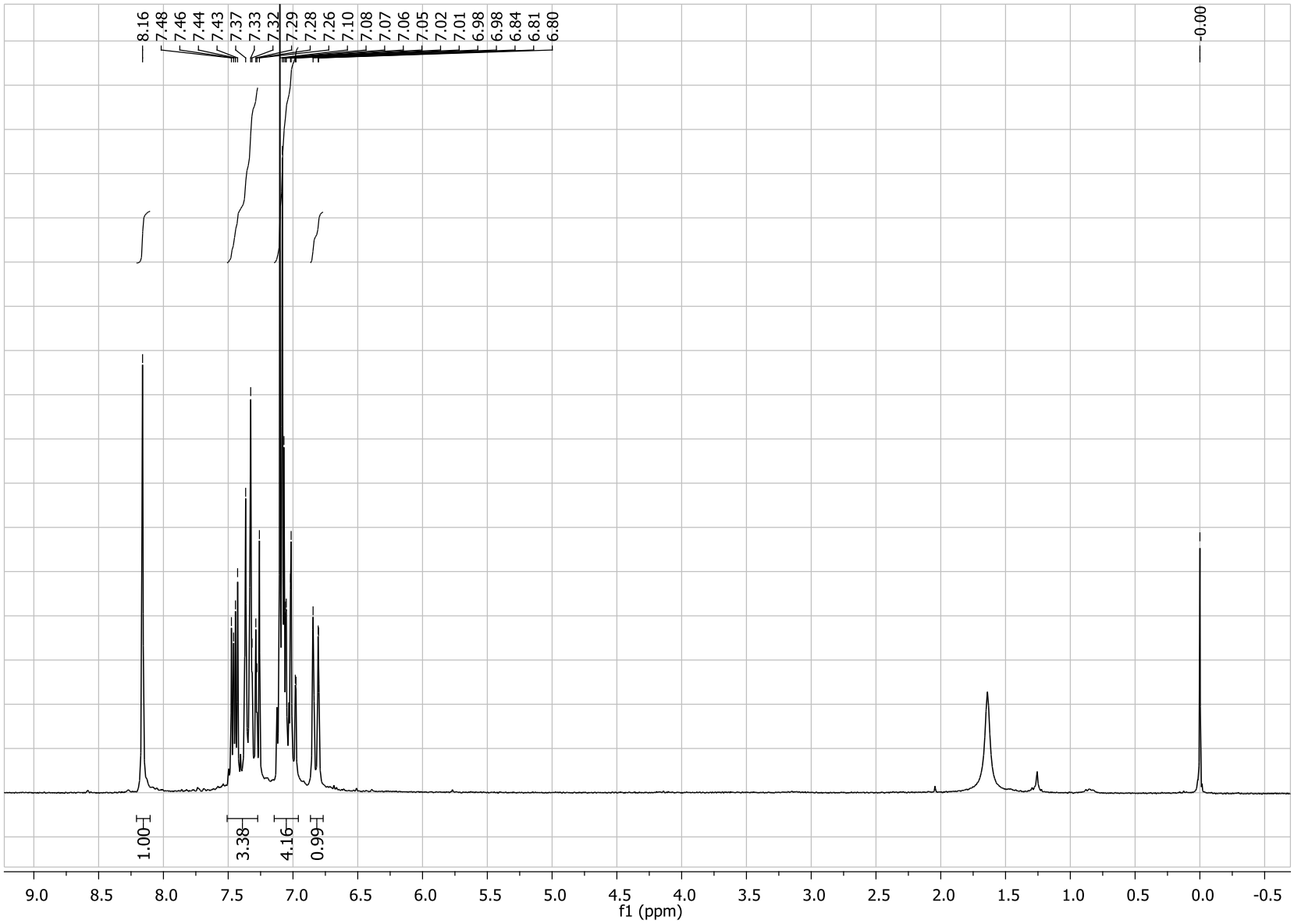


Figure S18. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4e**.

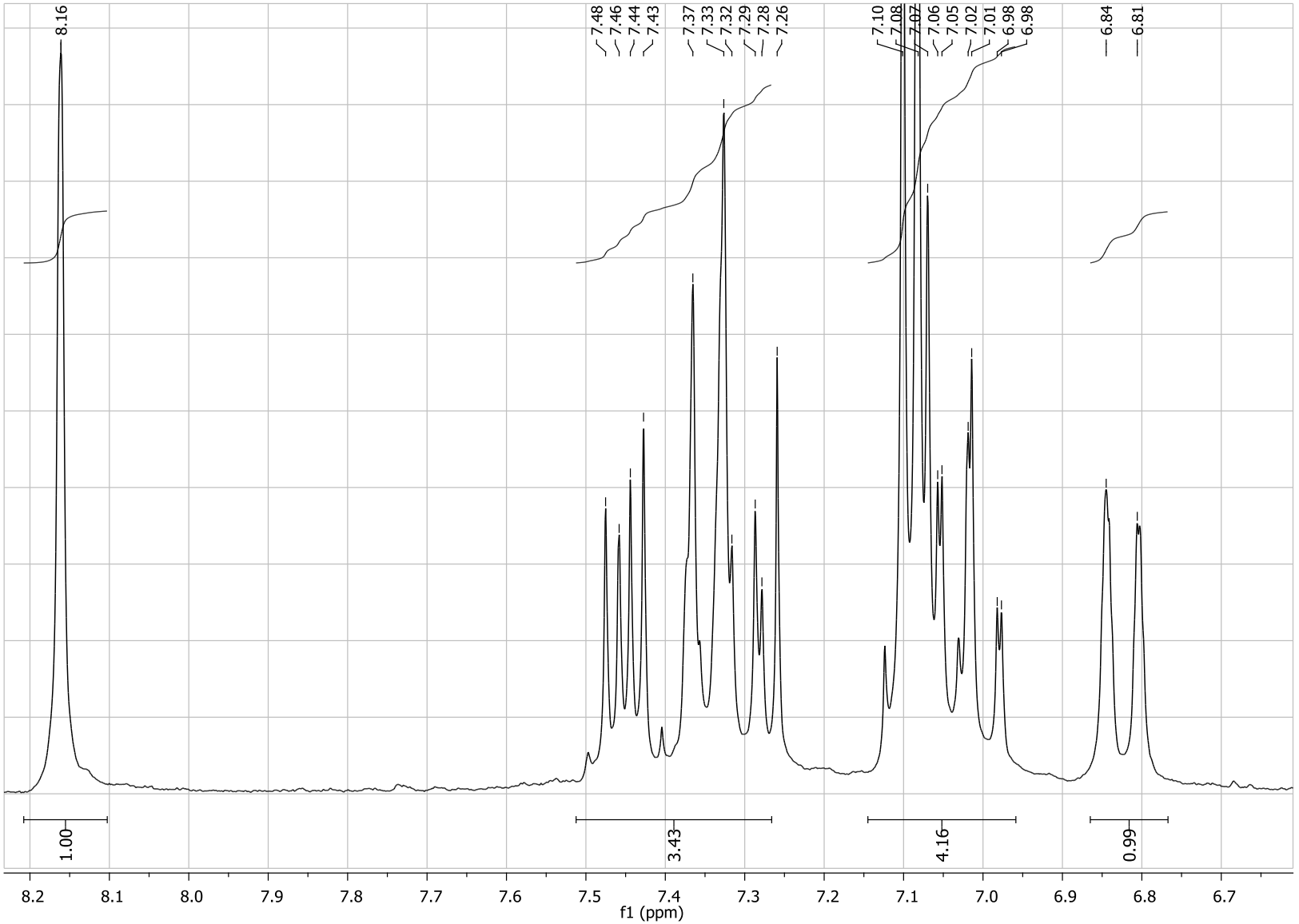


Figure S19. Expansion of ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **4e**.

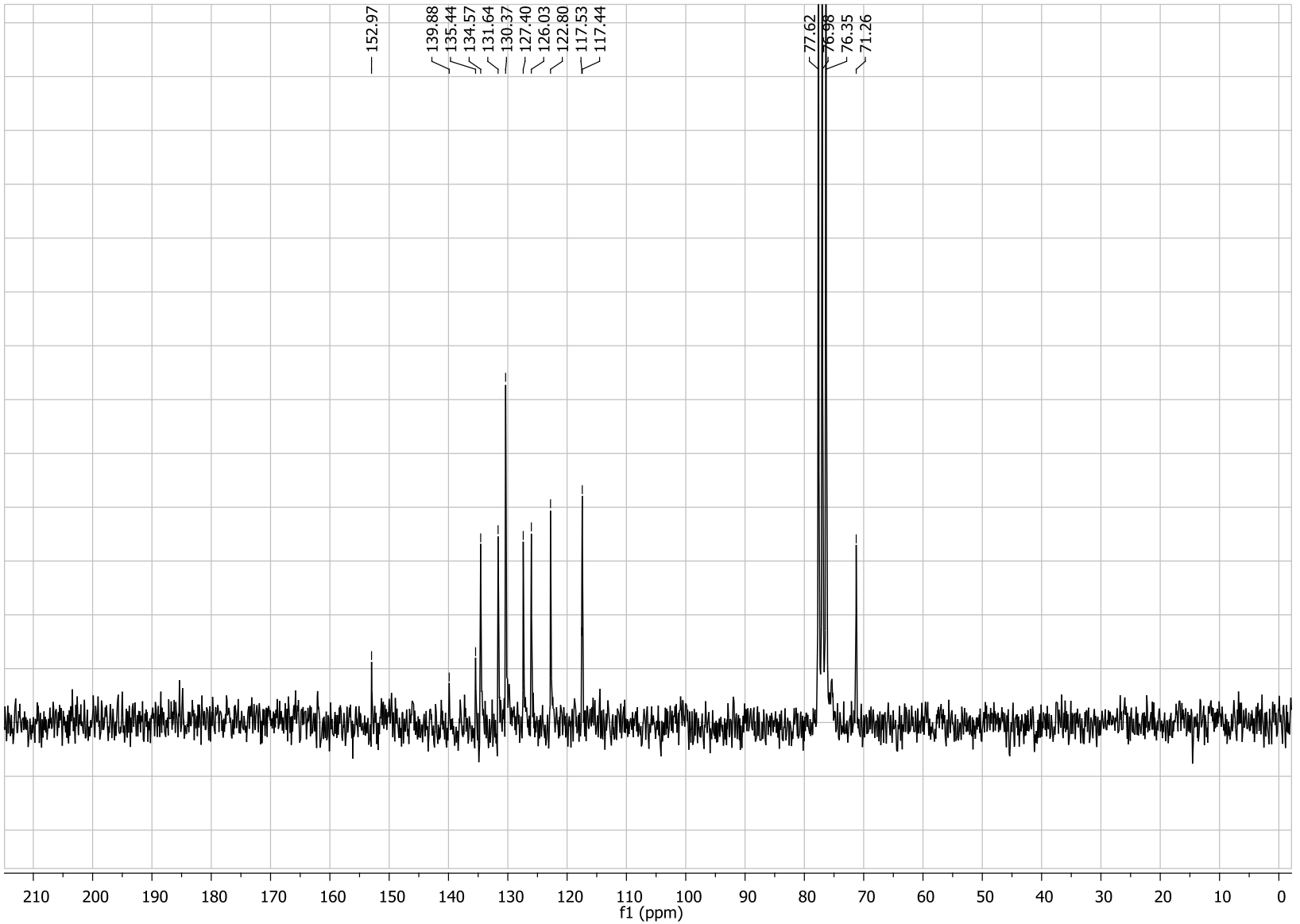


Figure S20. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **4e**.

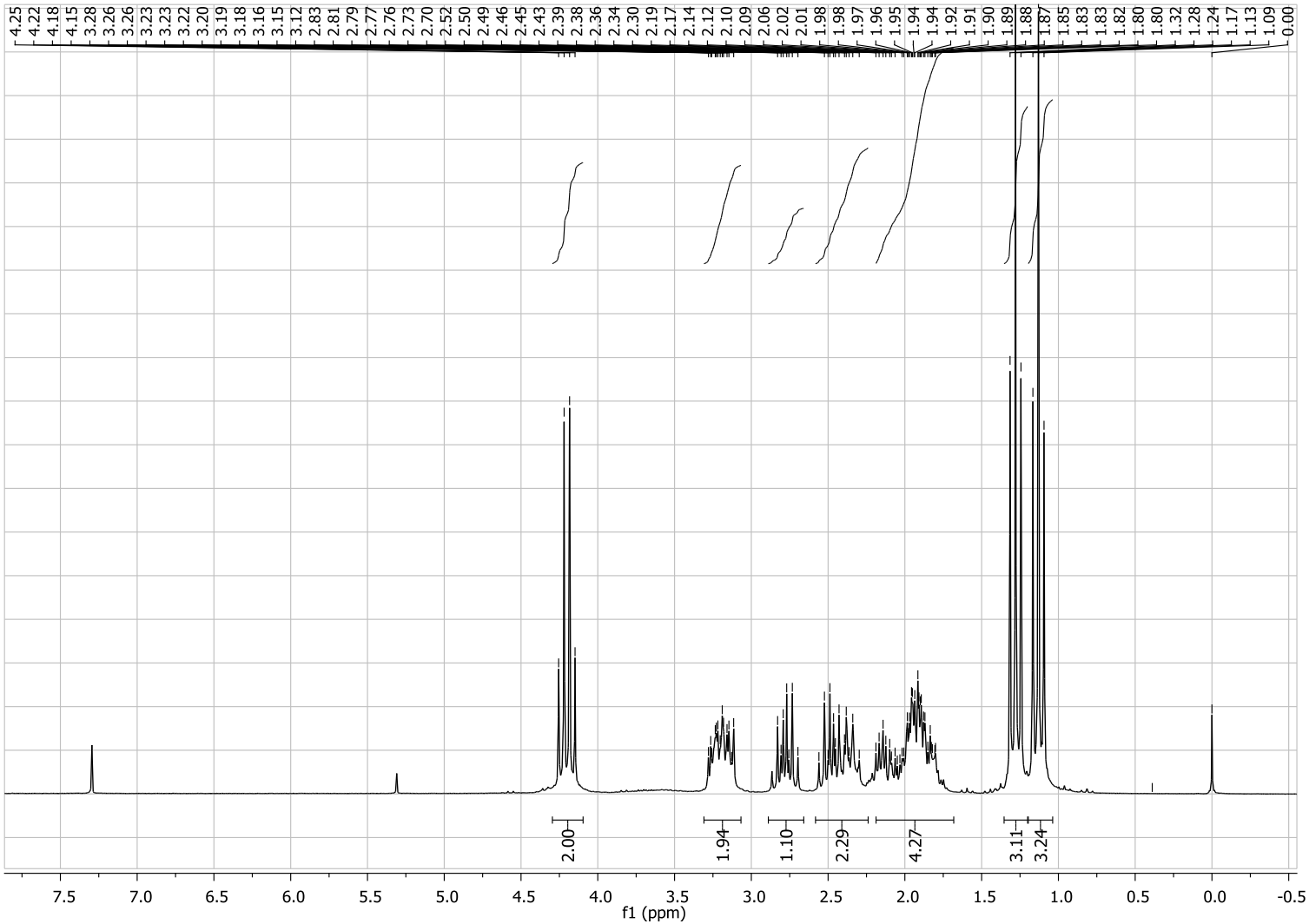


Figure S21. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **1a**.

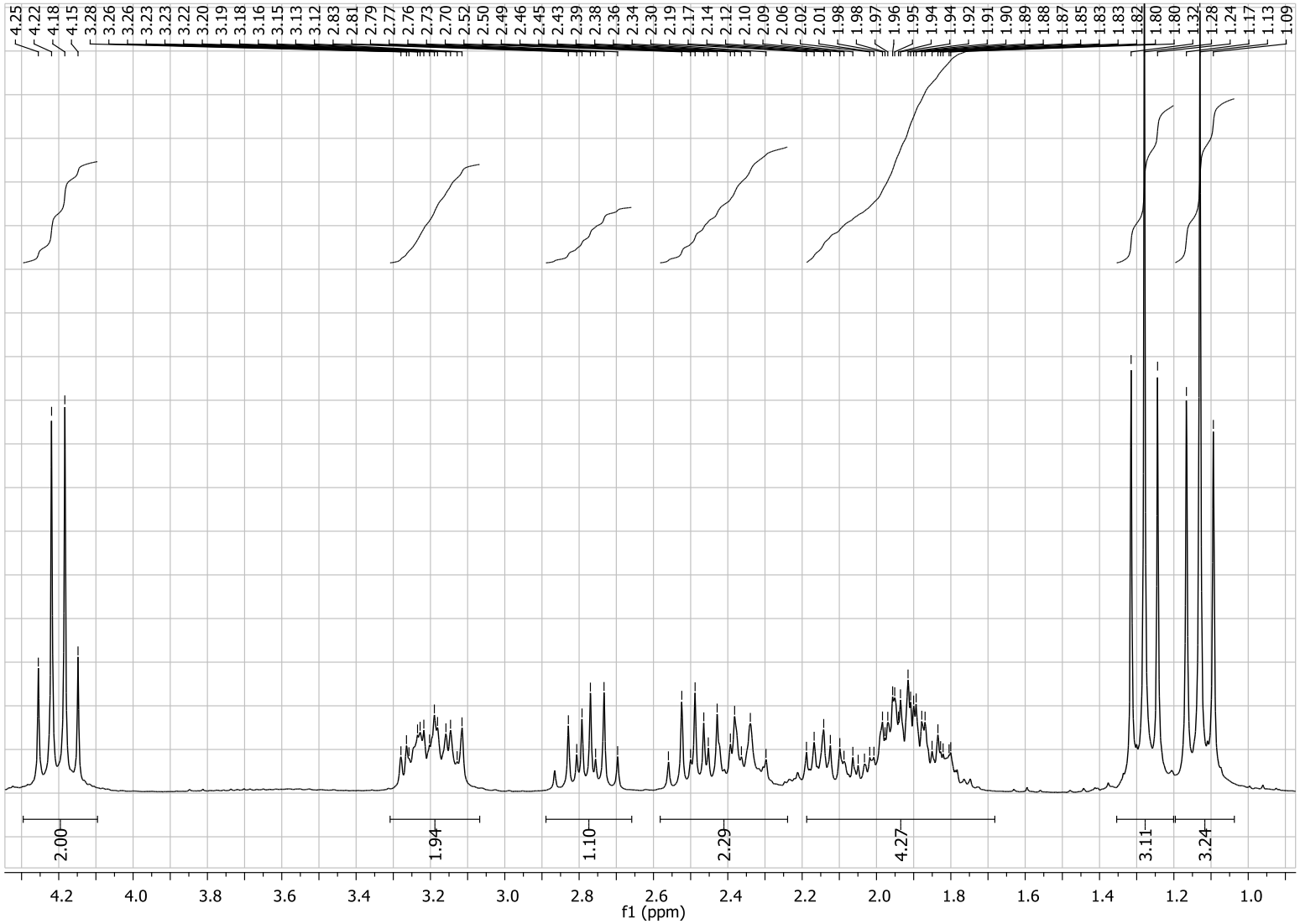


Figure S22. Expansion of ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **1a**.

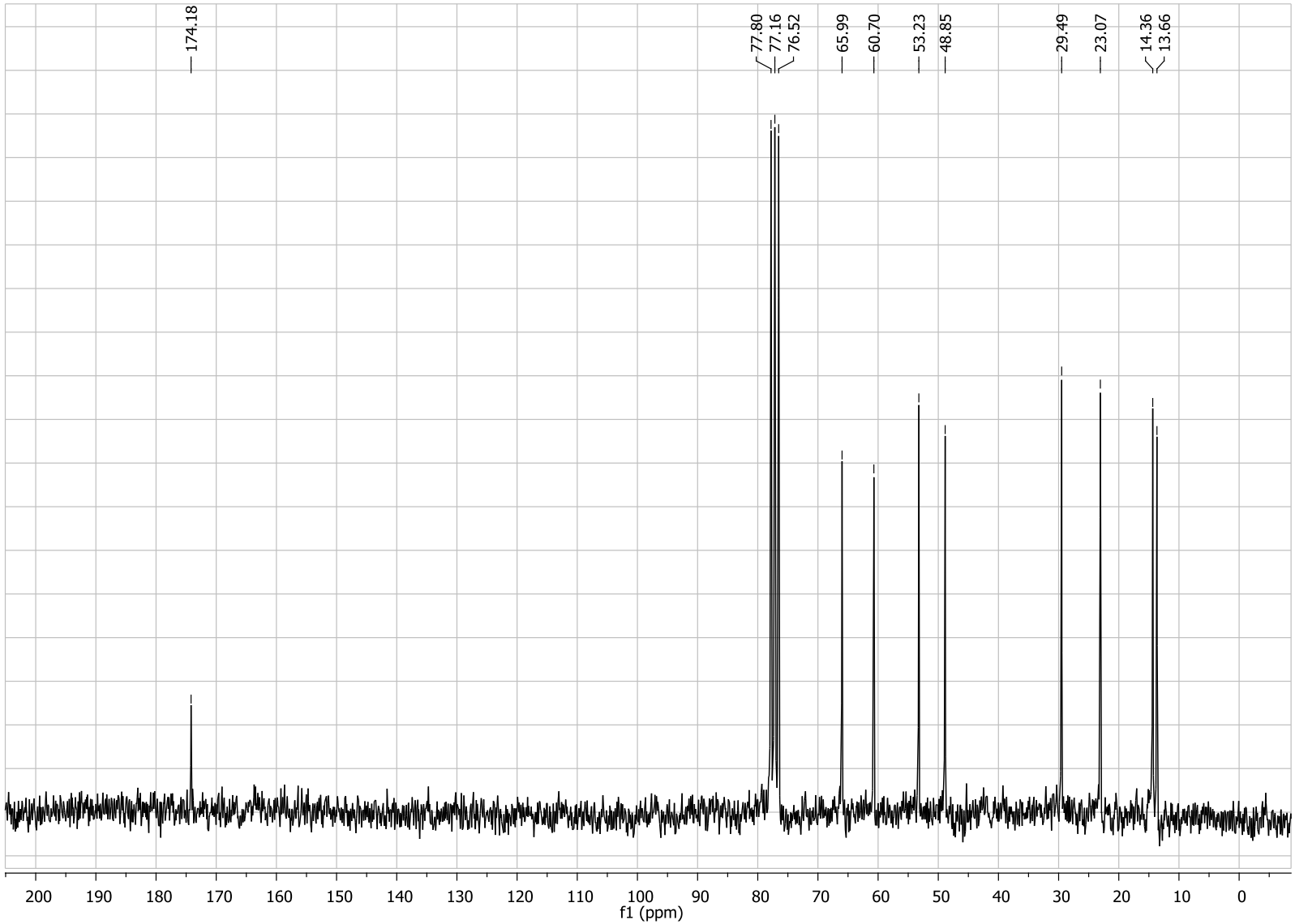


Figure S23. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **1a**.

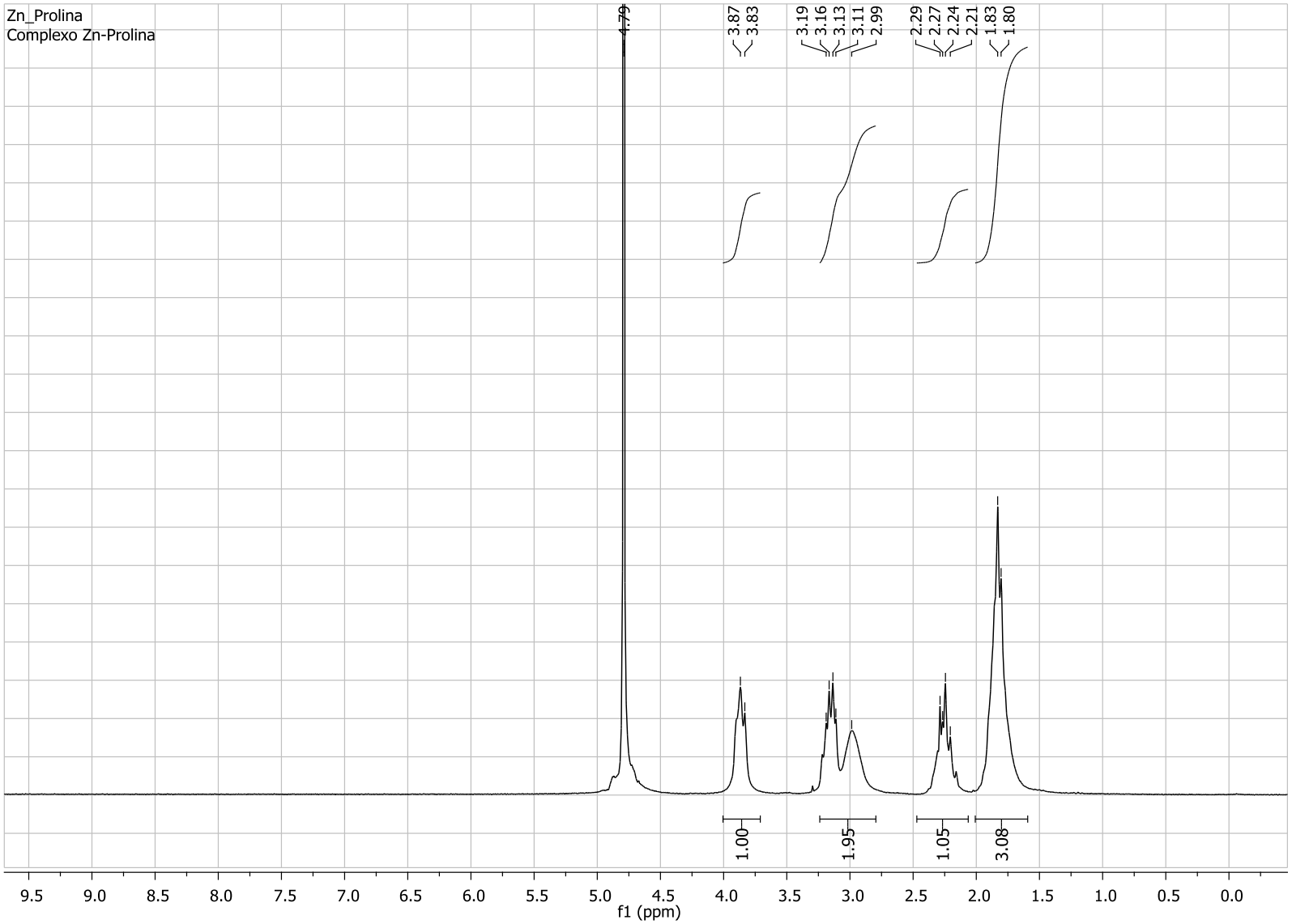
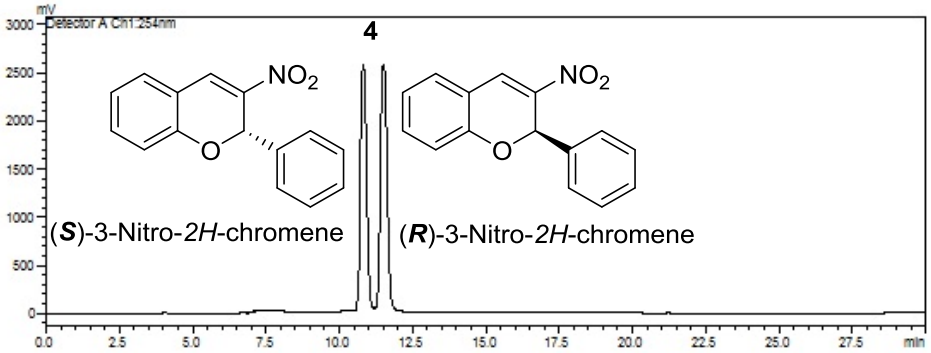
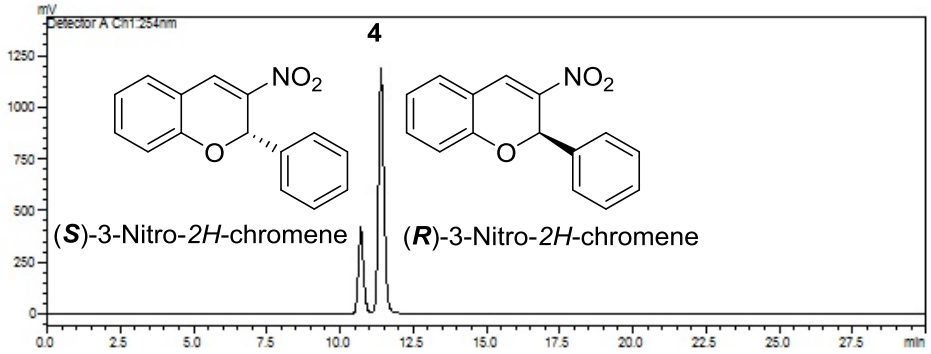


Figure S24. ^{1}H NMR spectrum (200 MHz, D_2O) of compound **1b**.



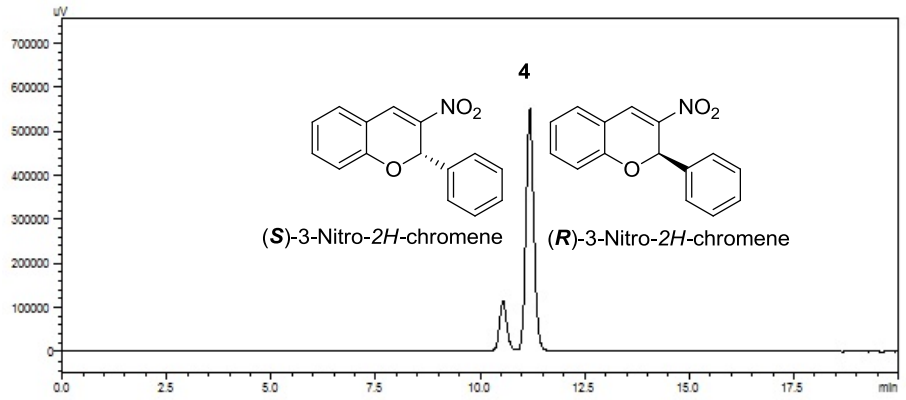
ID#	Ret. Time	Area	Height	Area%
1	10.554	6450405	520550	49.7691
2	11.455	6510251	499835	50.2309

Figure S25. HPLC of racemic compound **4**.



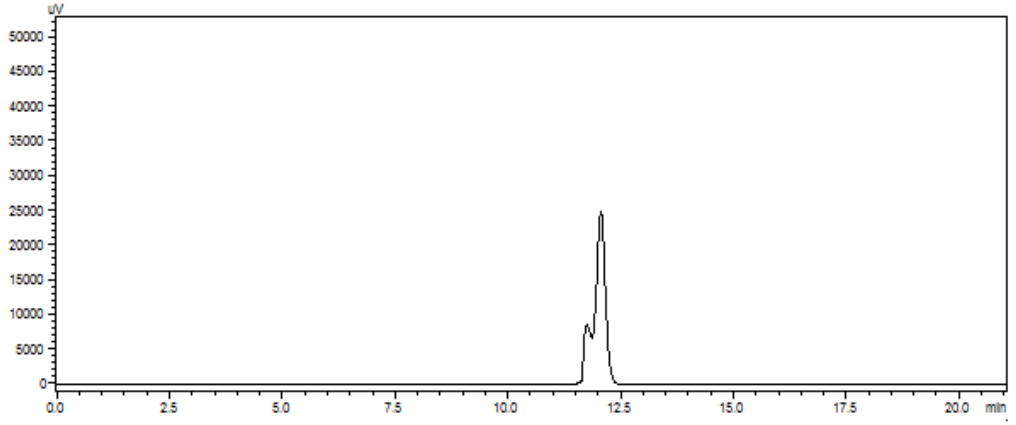
ID#	Ret. Time	Area	Height	Area%
1	10.536	455232	38976	22.5210
2	11.367	1566133	117976	77.4790

Figure S26. HPLC of 55% ee compound **4**.



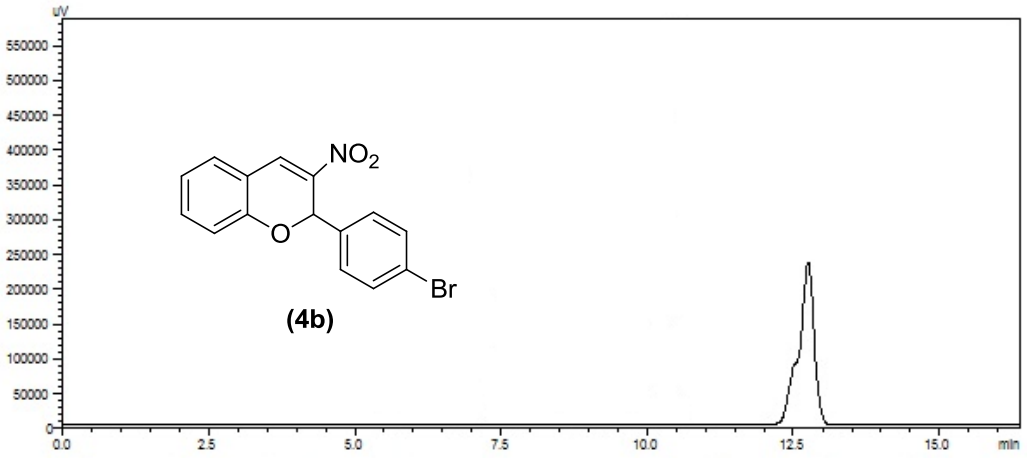
ID#	Ret. Time	Area	Height	Area%
1	10.524	162280	14496	14.7232
2	11.171	939931	73629	85.2768

Figure S27. HPLC of 70% ee compound **4.**



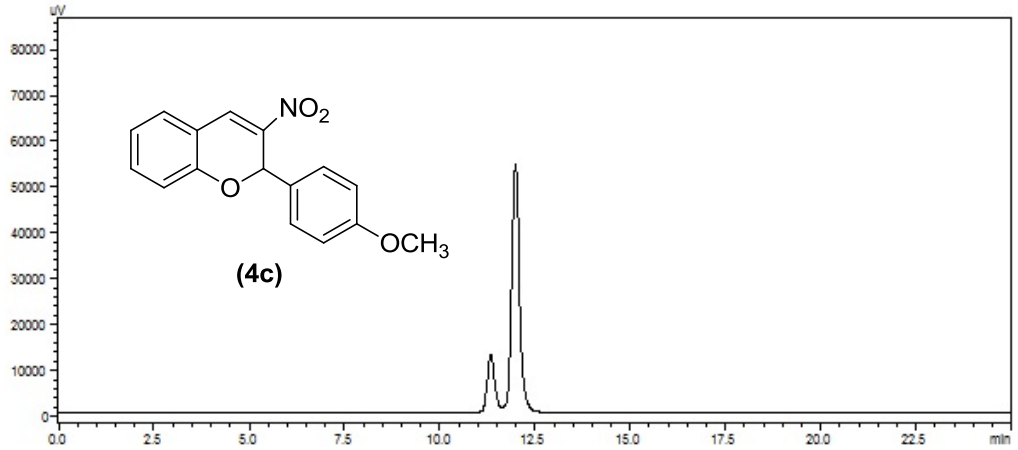
ID#	Ret. Time	Area	Height	Area%
1	11.788	293773	23161	19.8168
2	12.091	1188676	89073	80.1832

Figure S28. HPLC of 60% ee compound **4a**.



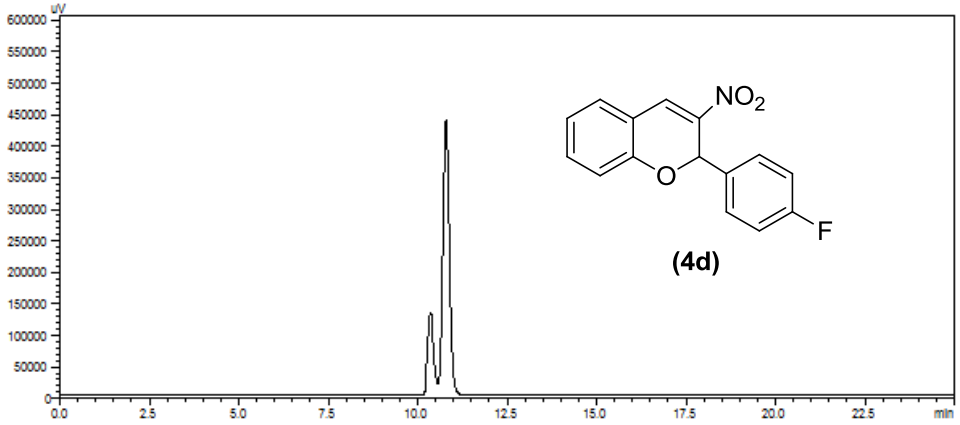
ID#	Ret. Time	Area	Height	Area%
1	12.592	1195947	110811	25.0504
2	12.751	255546	255546	74.9496

Figure S29. HPLC of 50% ee compound **4b**.



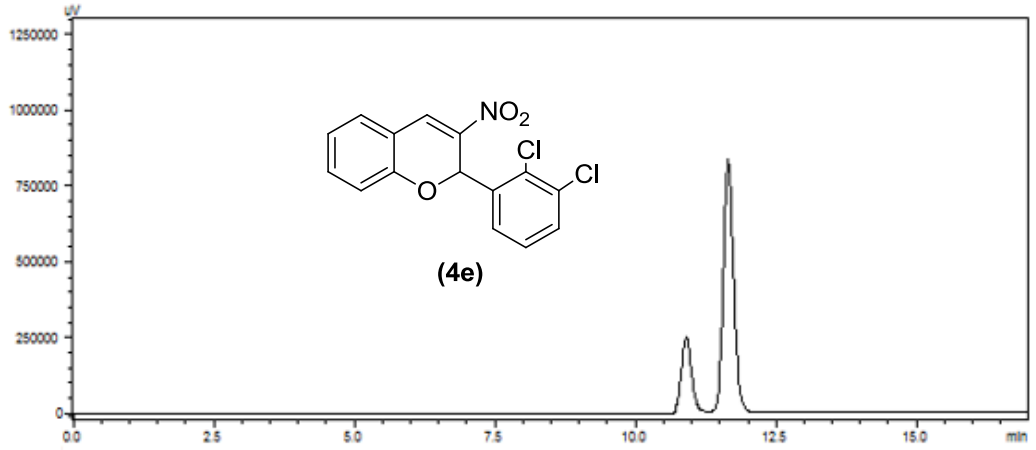
ID#	Ret. Time	Area	Height	Area%
1	11.340	161921	12962	14.7023
2	11.986	939410	61535	85.2977

Figure S30. HPLC of 70% ee compound **4c**.



ID#	Ret. Time	Area	Height	Area%
1	10.347	1250956	117367	19.5024
2	10.783	5163422	421160	80.4976

Figure S31. HPLC of 61% ee compound **4d**.



ID#	Ret. Time	Area	Height	Area%
1	10.903	3205356	270512	21.4197
2	11.651	117599161	907486	78.5803

Figure S32. HPLC of 57% ee compound **4e** (note: 40 °C).

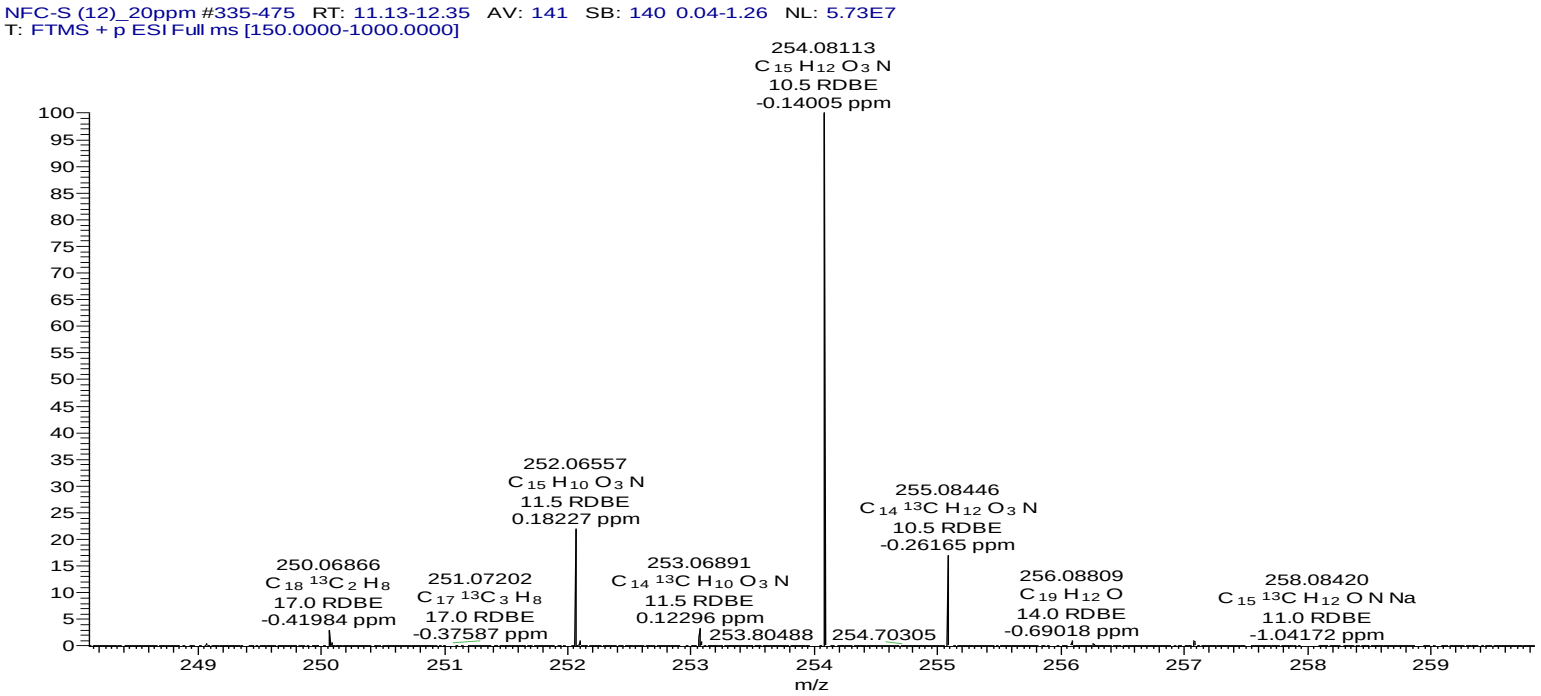


Figure S33. HRMS (ESI+) of compound **4**.

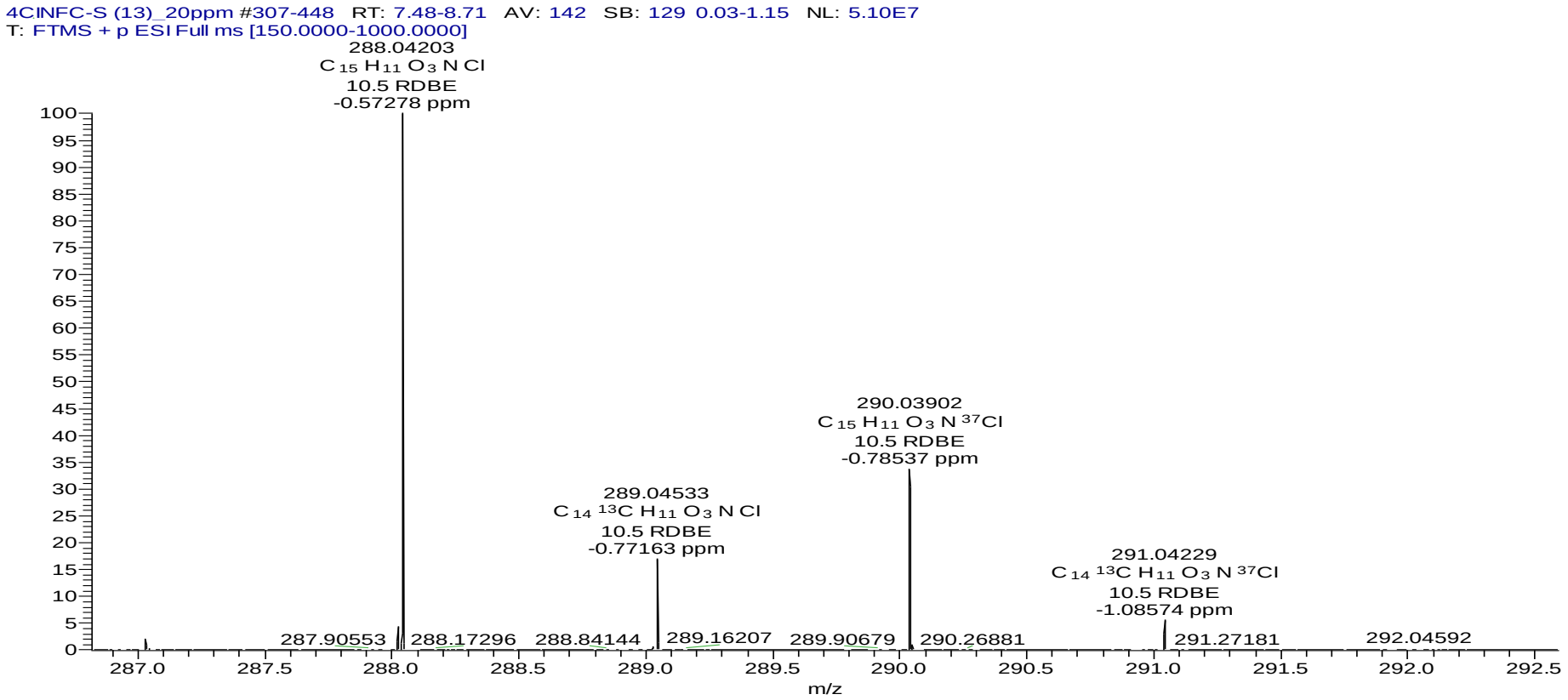


Figure S34. HRMS (ESI+) of compound **4a**.

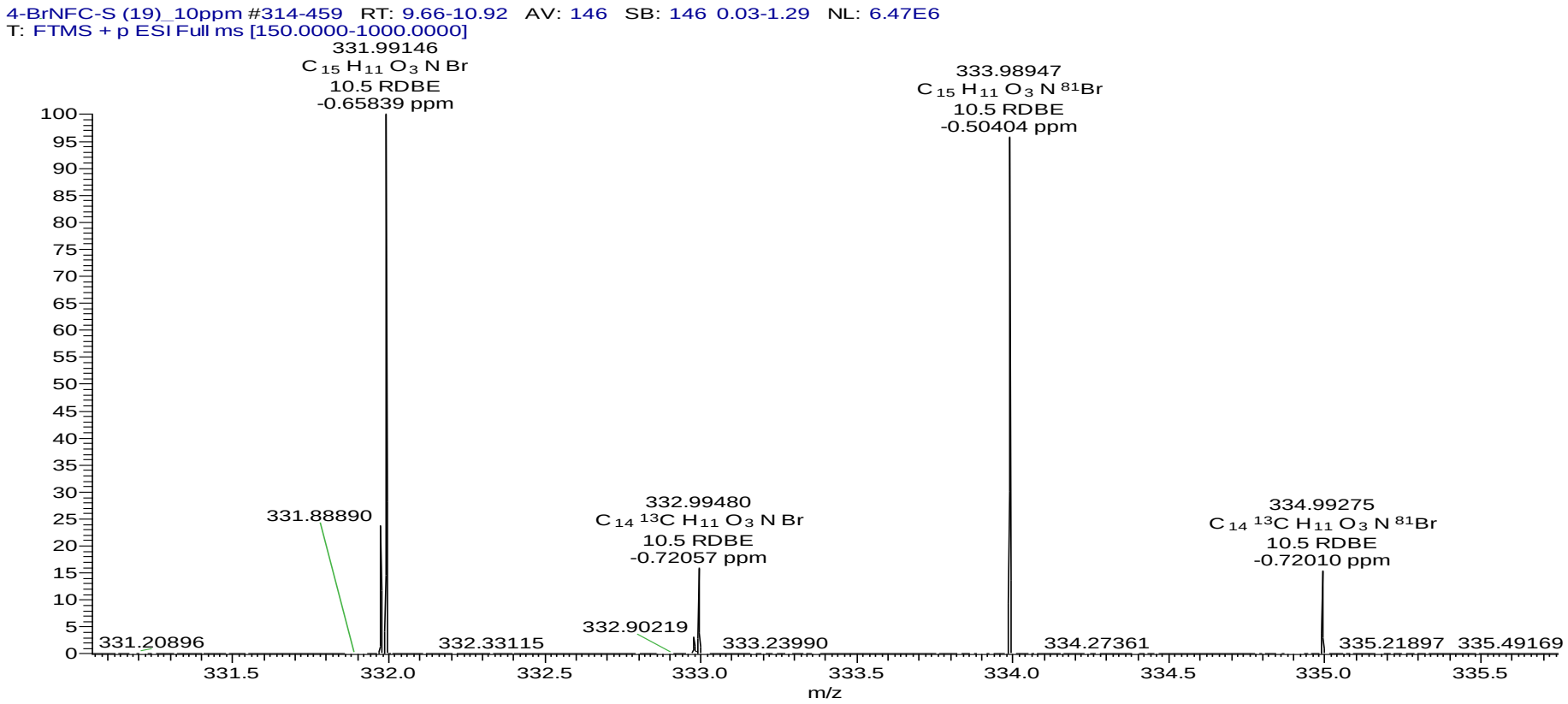


Figure S35. HRMS (ESI+) of compound **4b**.

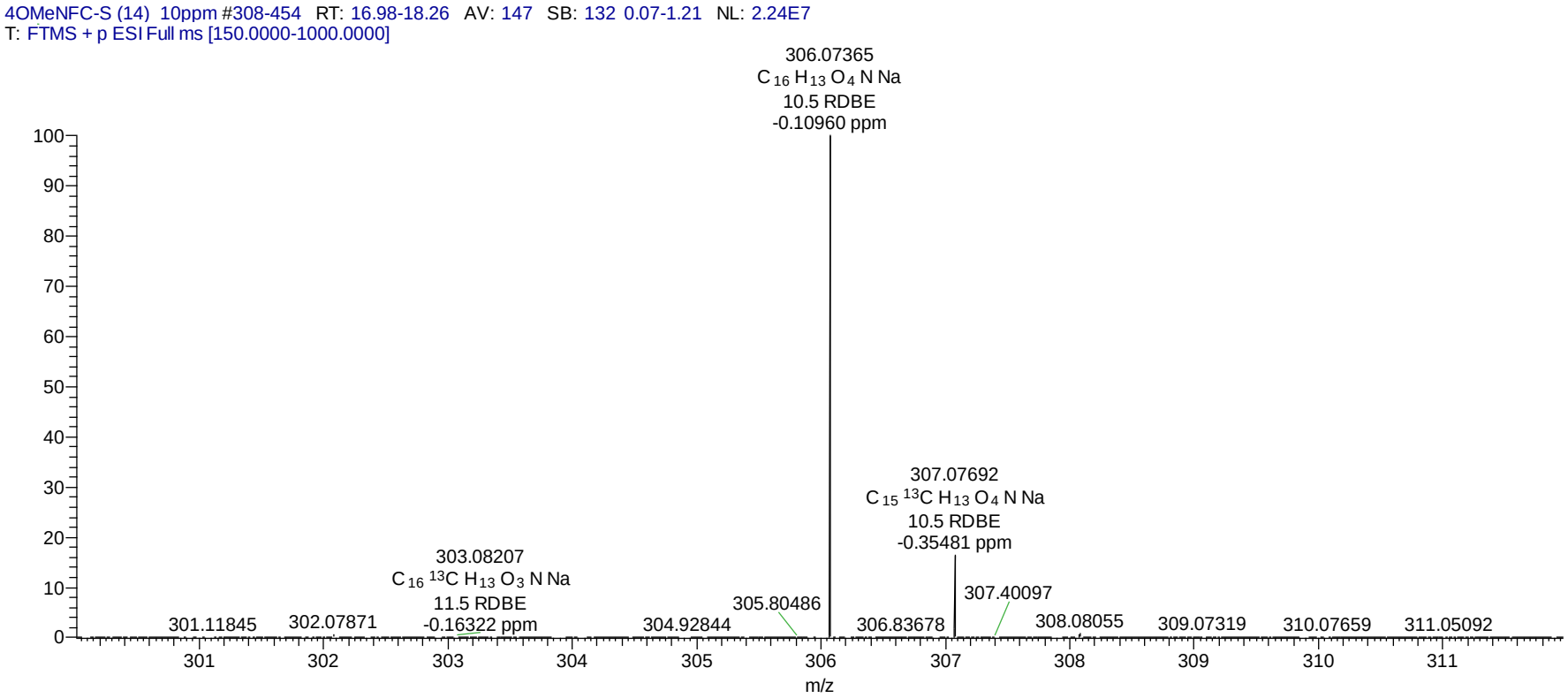


Figure S36. HRMS (ESI+) of compound **4c**.

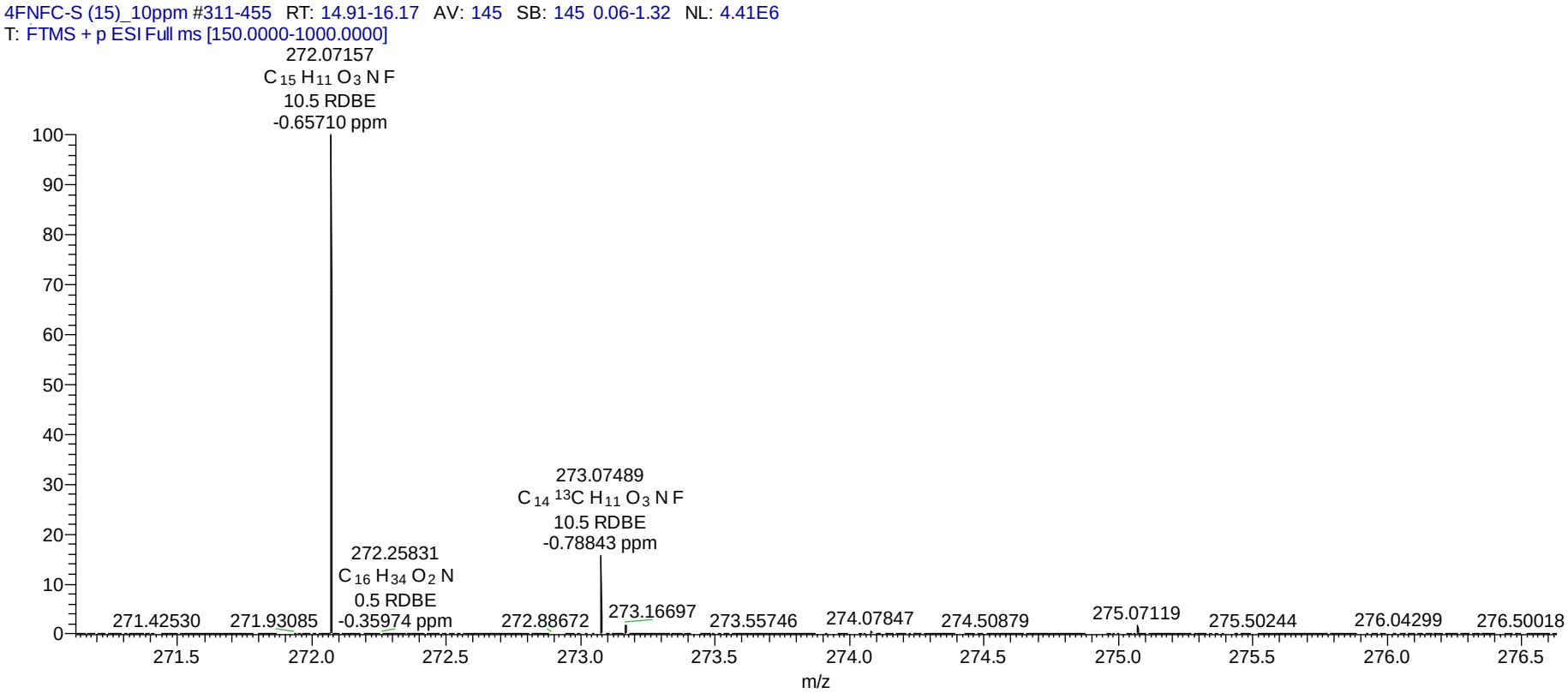


Figure S37. HRMS (ESI+) of compound **4d**.

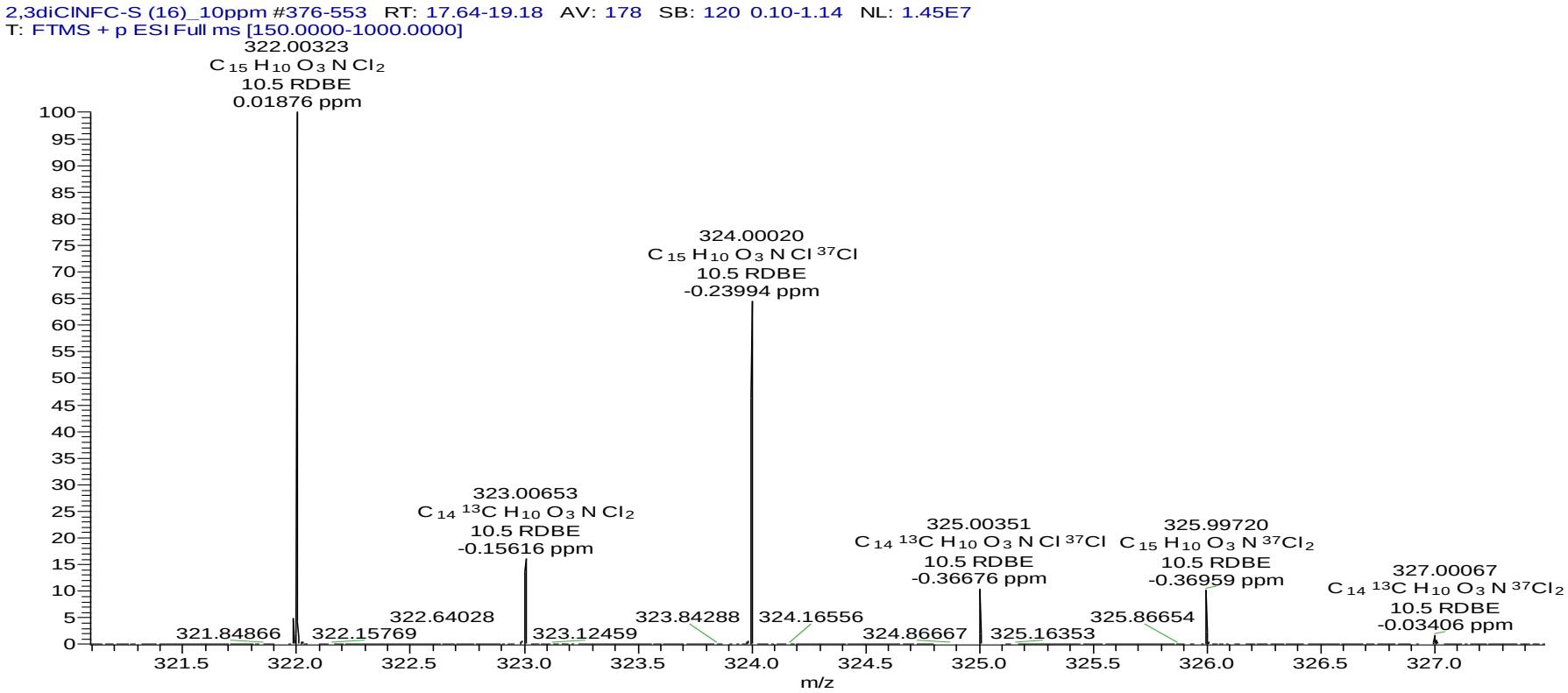


Figure S38. HRMS (ESI+) of compound **4e**.